THE PHOTOFUNCTIONALIZATION OF STEROIDAL 18-METHYL GROUPS

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ABSTRACT

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Sir George Williams University, 1973.

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The functionalization of the 18-methyl group of a number of steroids which could be utilized as synthetic precursors for batrachotoxin is described. For this purpose photolysis of a series of 20-nitrite esters was examined. The photolysis products were obtained in better yield than previously reported in 20β-nitrite ester series. An attempt was also made to assess effects of various structural parameters on the yields of the 18-functionalized steroids.

Previously described methods of preparing 20α- and 20β-steroidal alcohols were utilized and an improved method for the separation of 20-ols from an epimeric mixture is discussed.

Syntheses with model compounds having a C/D ring junction, similar to that encountered in batrachotoxin, were also undertaken.

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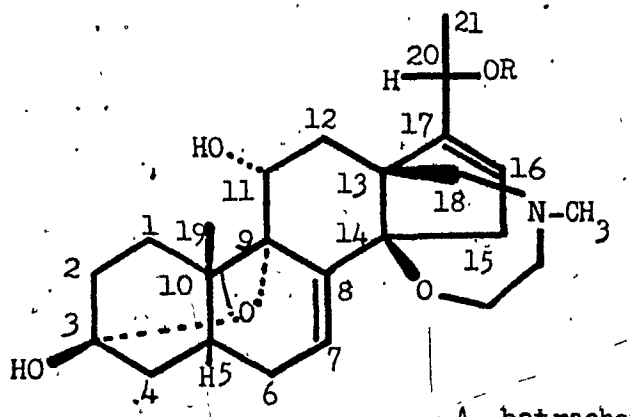
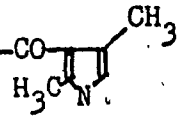
INTRODUCTION

In 1968 Witkop and his coworkers[1,5] described the isolation and structure of a new steroidal alkaloid, batrachotoxin(Fig. I, A), obtained from the skin secretions of a small, brightly colored Colombian frog of the genus Phyllobates aurotaenia.* The chemical, physical, biological,[1b] and pharmacological properties[6] of the compound have been



A, batrachotoxin R= 

B, batrachotoxinin A R=H

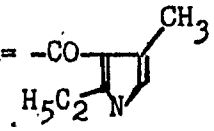
C, homobatrachotoxin R= 

Fig. I

examined in some detail. They reveal its ability to depolarize muscle membranes and cause neuromuscular blockade in concentrations of the order of 10^{-8} M, making it one of the most toxic substances known (Table I).[3,6]

Batrachotoxin, 3α,9α-epoxy-14β,18β-(epoxyethano-N-methylimino)-5β-pregna-7,16-diene-3β,11α,20α-triol 20-(2,4-dimethylpyrrole-3-carboxylate), has a number of unusual structural features.[5b] They

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* Previously referred to as Phyllobates bicolor.[2]

Table I. Toxic Substances with Their LD_{50} for Subcutaneous Administration in Mice.

Substance	LD_{50} μg/kg
Batrachotoxin(A)	2
Homobatrachotoxin(C)	3
Batrachotoxinin A(B)	1,000
Tetrodotoxin	8
Bufotalin	400
Strychnine	500
Sodium cyanide	10,000

include: i) the 3β-hemiketal, ii) the 3α,9α-oxide linkage, iii) the seven-membered 14β,18β-epoxyethano-N-methylimino ring, iv) the double bond at C_{16}, and finally v) the 2,4-dimethylpyrrole-3-carboxylate moiety at C_{20} -constituting features which pose many interesting biogenetic and phylogenetic questions. The synthesis of this complex substance has been a challenge to steroid chemists, which has recently been met by Wehrli who in a series of papers[7] has described a synthesis of the parent alcohol batrachotoxinin A(Fig. I, B) from a C_{18}-oxygenated steroid(Fig. II).

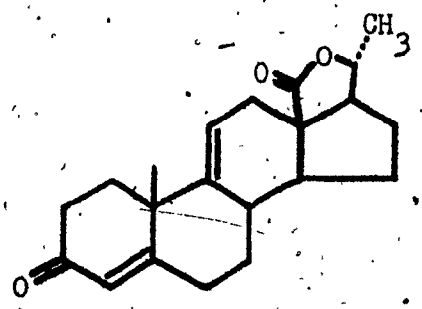

Fig. II

The objective of this work will be to investigate the photofunctionalization of the 18-methyl group of a series of readily available steroids, with a view to obtaining substances which will serve as suitable intermediates for a new synthesis of batrachotoxin. In particular, our efforts will concentrate on the photolysis of 20-nitrite esters--the Barton reaction--[15a] since it offers a means of direct introduction of a nitrogen atom bonded to C_{18} of the steroid nucleus.

Methods of Functionalization of Steroidal 18-Methyl Groups.

The functionalization of an angular methyl group and other inactivated skeletal positions in the steroid nucleus has been accomplished in a number of ways,[8a;11] principally by generating free radicals or similar reactive species* in close proximity** to the center to be attacked. The attacking moieties have been generated by fragmentation of N-haloamines, azides, hypohalites, and nitrites. The functionalization of the 18-methyl group has also been achieved by the action of lead tetraacetate on 20-ols and by irradiation of 20-carbonyl compounds.

Irradiation of a 20-N-chloroamine yields an 18,20-imine or amine bridge, the Hofmann-Loeffler-Freytag reaction(Scheme 1a).[8] Thermal decomposition of a 21-diazo-20-ketone provides an 18,21-cyclo steroid

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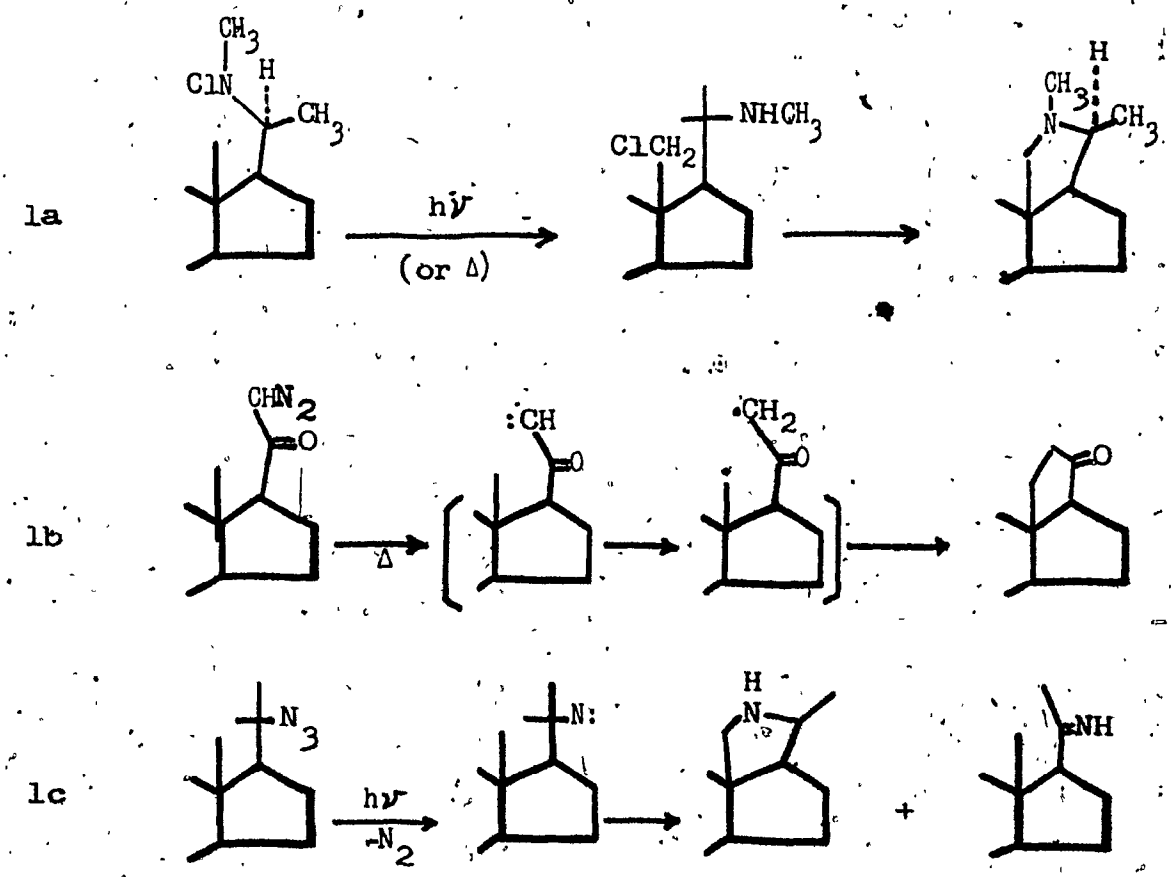
* Diradicals such as uncoupled carbonyl, carbene, or a cationic species such as RO^+ have been employed.[11b]

** Recently remote free radical halogenation at the inactivated tertiary positions,[21a] C_9 or C_{14}, and hydroxylation at C_5 or C_{14}[21b] as well as other remote oxidations[21c] of steroids have been reported.

(Scheme 1b),[9] while irradiation of the 20-azido steroid yields conessine (1c).[10] Photolysis or pyrolysis of 20-hypochlorites has yielded 18-chloro-20-hydroxy compounds(1d),[16] while photochemical rearrangement of 20-nitrite esters gives 18-oximes(1e).[15] Lead tetraacetate treatment* of 20-hydroxy steroids forms an 18,20-cyclic ether(1f),[13] but in the presence of iodine(hypoiodite reaction)** formation of a mixture of a

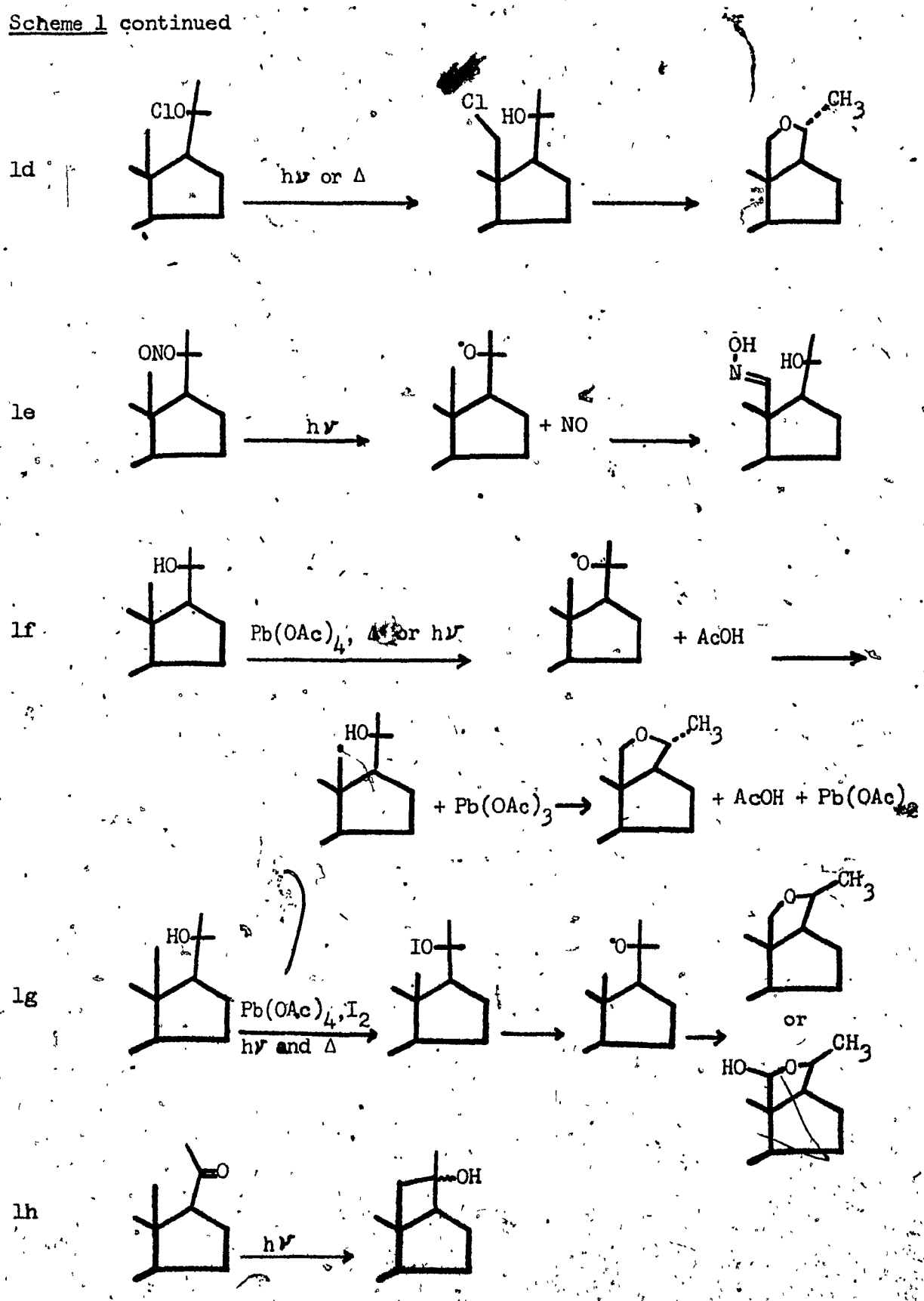
Scheme 1



* By thermolysis or photolysis.

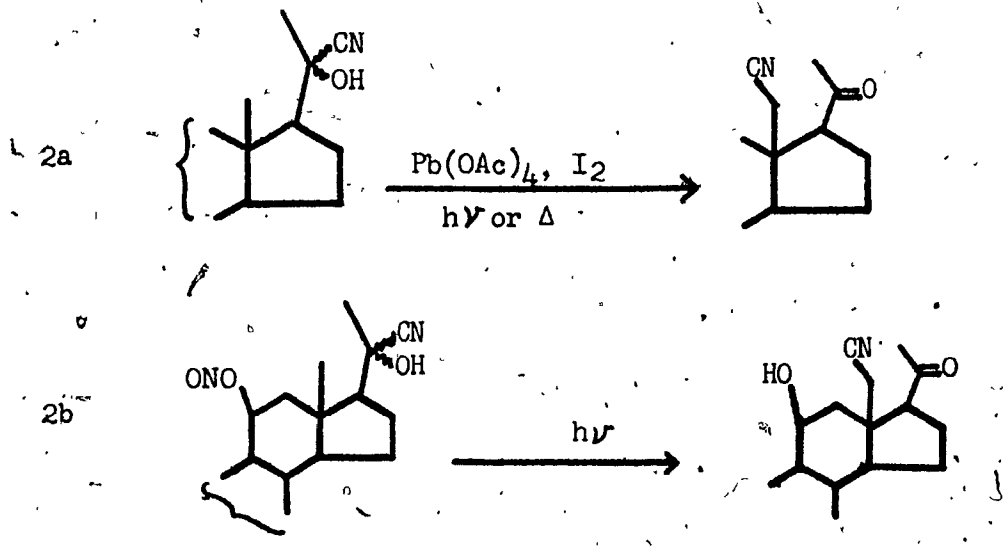
** Hypoiodites can also be generated by treatment of alcohols with t-butyl hypochlorite/iodine.[19] Mercuric oxide and iodine also can be used.

Scheme 1 continued



cyclic ether and a lactol has been reported(Scheme 1g).[14] Irradiation of the 20-keto steroid provides the 18,20-cyclo-20-ol(1h).[11a,12]

A number of photochemical exchange reactions accompanying angular methyl group functionalization have also been observed. The 20-cyanohydrins yield 20-keto-18-cyanosteroids(Scheme 2a)[13b] under photochemical or thermal conditions and a 20-cyanohydrin-11β-nitrite ester gives an 18-cyano-20-ketone(2b)[17] by photolysis.

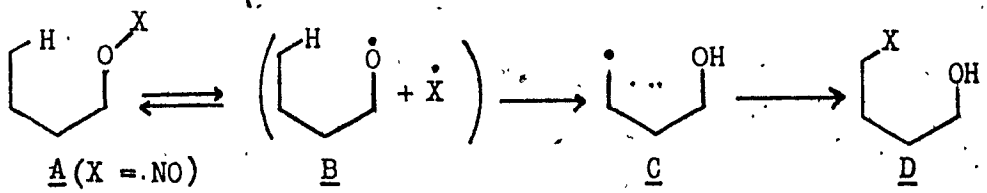


Scheme 2

Among these processes, the nitrite ester photolysis(Scheme 1e) and hypoiodite reaction(Scheme 1g) can be considered as the most versatile. They have in the past been exploited in steroid chemistry where the spatial arrangements of the rings and the distances between substituents are largely fixed. The former reaction as stated earlier is of particular interest in that it offers the possibility of direct introduction of a nitrogen atom at C_{18}.

Mechanism of Nitrite Ester Photolysis(Barton Reaction).

The mechanism[18] of the Barton reaction[15a,b] has been explained as one involving a "non-cage," free radical process with reversible photochemical homolysis of the O-N bond(Scheme 3, X=NO).* Intramolecular hydrogen abstraction occurs through a six-membered transition state (B → C) and reassociation is accompanied by scrambling(C → D).



A(X = NO) B C D

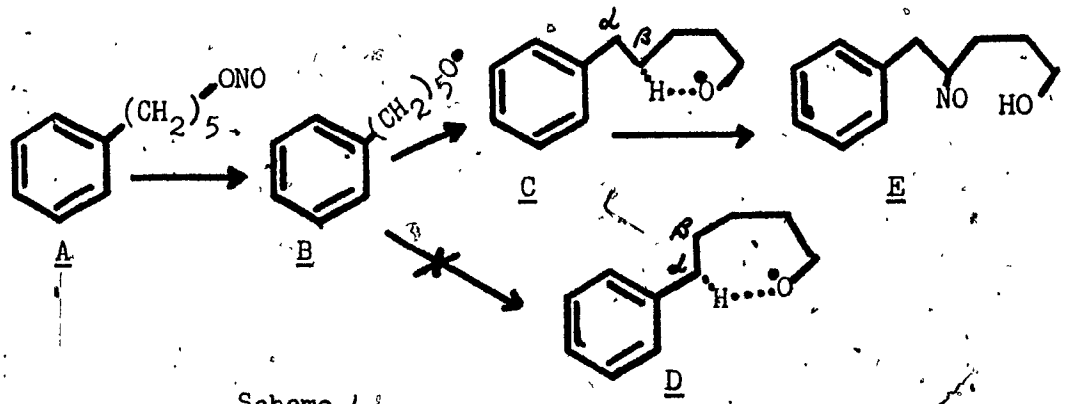
Scheme 3

The existence[11b] of an intermediate alkoxy radical B is inferred from the observation that photolysis of an ^{15}N-containing steroidal nitrite ester in the presence of an excess of ^{14}N-containing t-butyl nitrite resulted in the recovery of the steroid containing a very high proportion of ^{14}N(^{15}N : ^{14}N = 1.0 : 3.45).[18a]

The initial reversible step A ⇄ B(Scheme 3) proceeds via geminate recombination under normal photochemical conditions. The reversibility is further supported by the observation that the below unity quantum yields of NO[22]—due to the reversible nature of the reaction—fall still lower in the presence of excess nitrite due to the suppression of the forward reaction(A → B).[11b] It has also been noted that the quantum yield of oxime falls under these conditions.[15b] The separation of the radicals was noted in the subsequent stage(B → C) and thus the end product D or its equivalent does not show a "cage" effect.

* X may be halogen, NO_2, OR, and other substituents which permit homolytic fission upon photochemical activation.[15a,b]

Step B → C has been demonstrated to be an intramolecular hydrogen abstraction by alkoxy radical through a six-membered cyclic transition state[26a,b] for both rigid and mobile aliphatic nitrites. The existence of this transition state was conclusively demonstrated by Kabasakalian et. al.[26a] Photolysis of 5-phenyl-1-pentyl nitrite(Scheme 4) was shown to yield exclusively 4-nitroso-5-phenyl-1-pentanol(E) involving abstraction of a hydrogen beta to the phenyl group. This process occurs, although it is energetically less favoured than the abstraction of an activated α-hydrogen by some 16.5 kcal./mole. It appears, therefore, that the steric requirements of the transition state are of greater importance. Furthermore Kabasakaliam and Townley[26b] have reported that the geometric factor dominates the structural factor when primary hydrogen atoms are involved in the Barton reaction, while the inverse is true when secondary hydrogen atoms are involved.



Scheme 4

The precise spatial arrangement of the intermediate B(Scheme 3) has not been demonstrated, but the chair(Fig. III, A), boat(B), or quasi-chair(C) forms can be considered. Among these forms, the last has been shown to be the most favorable, providing maximum orbital overlap*, according to the results obtained from a rigid steroid system.[24] All reactions in which the reacting centers are fixed as constituents

of a six-membered chair-like ring, proceed with good yield.[23]

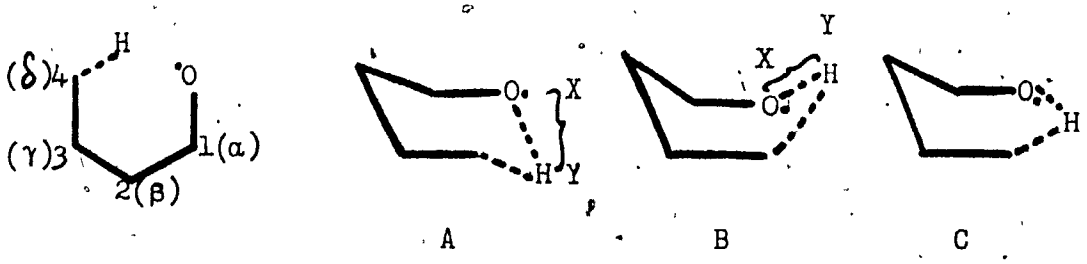


Fig. III

Important also for efficient intramolecular hydrogen abstraction is the distance X–Y, which must fall between certain critical limits. The activation energy for the abstraction reaches a minimum in rigid systems with an $O\cdot\rightarrow C_4$ distance of from 2.5 to 2.7 Å.[23] For distances exceeding 2.8 Å, the rate of intramolecular abstraction becomes smaller than that of the intermolecular process or other fragmentation reactions. If the distance is less than 2.7 Å between a number of competing sites, the rate of abstraction of hydrogen occurs in the order: tertiary > secondary > primary.[25,26c]

The internuclear distance between the oxygen radical and the hydrogen to be abstracted is 2.1 Å for an $O\cdot\rightarrow C_4$ distance of 2.6 Å. This condition is realized when the $O\cdot\rightarrow C_4$, C_1, and C_3 lie in the same plane in the steroid system.**

That the intramolecular attack is favoured over an intermolecular hydrogen abstraction was demonstrated by the photolysis of n-octyl

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* The maximum angle of C–H–O, which may be attained in the transition state of the most favorable Barton reaction, is 146°.[18c]

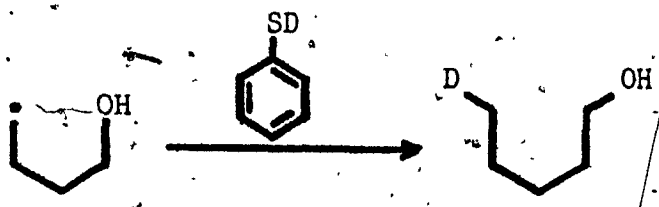
** Dreiding models give values of from 2.5 to 2.7 Å for the $O\cdot\rightarrow C_4$ distance for sites where there is no bond angle strain.[23]

nitrite in n-heptane by Kabasakalian and Townley.[22] The product ratio of 4-nitroso-1-octanol to all other nitroso heptanes is 4.5 : 1. The statistical ratio of the former—the intramolecular attack product—to the latter—the intermolecular attack products—should be about 1 : 252, if it is assumed all hydrogen abstractions are processes of comparable exothermicity.[18c]

The step C → D(Scheme 3) constitutes the association or combination of the alkyl radical with NO, furnishing the final product. In this step solvent does not readily participitate even when it is a good radical reactant like toluene.[15b] As observed earlier, the quantum yield for the photo-decomposition of nitrites is less than unity, while the chemical yield in the transformation A → D is high. These factors have been used as evidence that the process takes place within a solvent "cage." Contradicting this conclusion, the photolysis to half complete reaction of an equimolar mixture of ^{14}N- and ^{15}N-nitrite esters of differing steroids,[18a] gave oximes which were isotopically completely scrambled, whereas the unreacted nitrites recovered showed no significant scrambling of the isotopes.

Photolysis of a nitrite ester in the presence of S-deutereo-thiophenol, a good radical transfer reagent,[18b] gives the C-deutereo

(Scheme 3, C)



compound.[27] The addition of 5 % cumene did not affect the yield of the photoproduct.[15b] From these results the possibility of a chain reaction or the intermediacy of a long lived radical species has been ruled out.

The step A → B(Scheme 3) can be pyrolytically(in the gas phase) and photolytically induced.[20,33] However, pyrolysis of nitrites in the melt or in solution produces alcohols and ketones. Pyrolysis of nitrites under these conditions will be greatly influenced by traces of water or equivalent impurities(hydrogen donors), leading to thermal decompositions of an ionic type.[33]

Since the alkoxy radicals generated in solution by thermolysis of hypobromite[29] or from an alcohol in the presence of lead tetraacetate,[30] or by redox reactions of alkyl peroxides with ferrous ion[20a] also have a good capacity to abstract hydrogen from an appropriately placed carbon-hydrogen bond, it is assumed that an alkoxy radical is not generated in the pyrolysis of a nitrite ester in solution. The alkoxy radicals generated by these thermolyses reactions(in particular those generated by the redox reaction) are in contradiction to the theory that "activated" or "high energy containing" alkoxy radicals are involved.[11b,15a,b]

The discrepancy in the behaviour of nitrite esters under photochemical or thermal conditions must arise from the failure to generate alkoxy radicals under the latter conditions(in the melt or in solution) rather than any intrinsic difference between radicals from alternative sources. That the temperature[20a] was a factor for the differing behaviour of nitrite esters was also proved to be erroneous.[33]

The reactions of A → D(Scheme 3) may be summarized as follows:

i) The alkoxy radical and nitric oxide are generated reversibly in solution by photochemical means and the possibility that scrambling may have occurred in this step has been eliminated.

ii) The rearrangement from B to C is a rapid reaction. Free radicals

such as C may be suggested as moderately long lived intermediates in the Barton reaction.

iii) The process, however, is not a chain reaction and very long-lived alkoxy or carbon radicals are not involved.

iv) Other radical sources can intervene at the last stage (C → D), causing radical exchange processes.

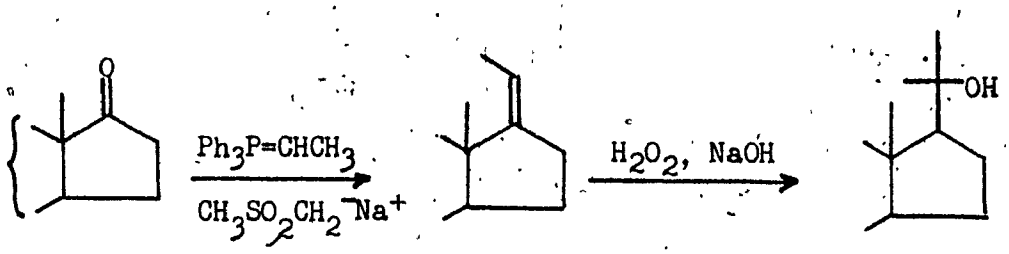
Methods of Preparation of 20α- and 20β-Hydroxy Steroids.

Implicit in the photolytic approach to the functionalization of 18-methyl groups by the Barton reaction, is the necessity of obtaining nitrite esters of 20α-hydroxy steroids, since it has been demonstrated that much better yields of the 18-oximino products are obtained from these rather than the 20β-isomers.

The reduction of steroidal 20-ketones by metals, complex metal hydrides, and by catalytic hydrogenation generally gives a mixture of 20α- and 20β-isomers, in various ratios, and the separation of a pure isomer from the product is difficult. It is generally easier to obtain the 20β-isomer in a higher yield than the corresponding α-isomer, since the reductions which favour a higher ratio of the β-isomer do so more stereoselectively than those which favour the 20α-isomer as a major product.

One reported method, which provides pure and a relatively good yield of 20α-ols, constitutes the conversion of a 17-keto steroid to an ethylidene derivative by means of a Wittig reagent, followed by hydroboration of the Δ^{17}-olefin (Scheme 5).[46]

Reduction of ketones with complex metal hydrides may be regarded as being initiated by the approach of the metal hydride anion towards



Scheme 5

one face of the carbonyl group, with subsequent transfer of a hydride ion to form a C-H bond. The complex metal hydride reduction of 20-keto steroids gives products which are invariably rich in the 20β-isomer.[36] The small difference in energy(0.2 to 0.25 kcal/mole in favour of the β-isomer)[41] between 20α- and 20β-ols, cannot by itself account for the product distributions observed. It would appear, therefore, that "steric approach control"[114] or "kinetic control," where the energies of the transition states for the competing reactions determine the product distribution, is operating.

The stable conformation of the 17β-acetyl group about the C_{17}-C_{20} bond places the carbonyl oxygen atom in a position nearly eclipsing C_{16} with the 21-methyl group lying in the vicinity of C_{12}(Fig. IV)[37] as

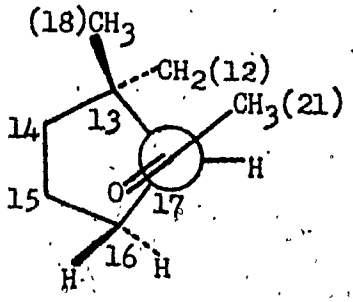


Fig. IV

assigned by dipole moment,[37a] stereochemical, and spectral evidence.[37b,c] Hydride attack on the β-face of the ketone is therefore restricted by the 18-methyl group and α-attack leading to the 20β-isomer predominates

(Fig. V).

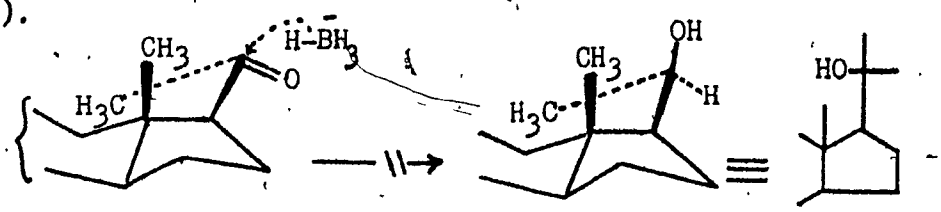


Fig. V

Reduction by alkali metals is believed to proceed by initial electron donation from the metal to the carbonyl group to form a carbanion, in which the carbonyl carbon atom is considered to have attained a tetrahedral configuration. In this state it rapidly assumes its preferred conformation and there is a notable preference for the formation of the more thermodynamically stable alcohol.[38]

For 20-hydroxy steroids, the 20β-isomer has a conformation[39] in which the C_{20}-H bond lies roughly parallel to the C_{13}-C_{18} bond and the substituents about C_{17}-C_{20} are thought to be fully staggered(Fig. VI).

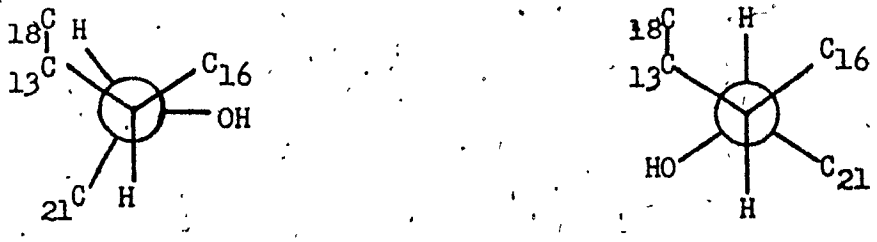


Fig. VI[39a]

In the case of the 20α-ol there is a slight twisting in order to relieve the nonbonded interaction between the 21-methyl group and C_{12}-methylene group(Fig. VI and XIV). Consequently the 20α-isomer is of slightly higher energy than the 20β-isomer. Therefore, cursory consideration of 20-keto steroids might suggest that their alkali metal reduction should yield the more stable 20β-ols, but this is contrary to

reported observations.[40]

Kirk and Mudd[41] investigated the reduction and clarified the stereochemical features and mechanisms by a conformational analysis of the reacting systems, Electron transfer to the more stable carbonyl conformer(Fig. VII, A) leads to either the structure B or C.* According to Barton's assumption[42] that the carbanion lone-pair is a smaller substituent than either oxygen or a methyl group, the configuration C is more stable than B, though it is unlikely that there will be a pronounced preference for either in view of the very small difference in stability between the two 20-ols. Therefore, if the key intermediate

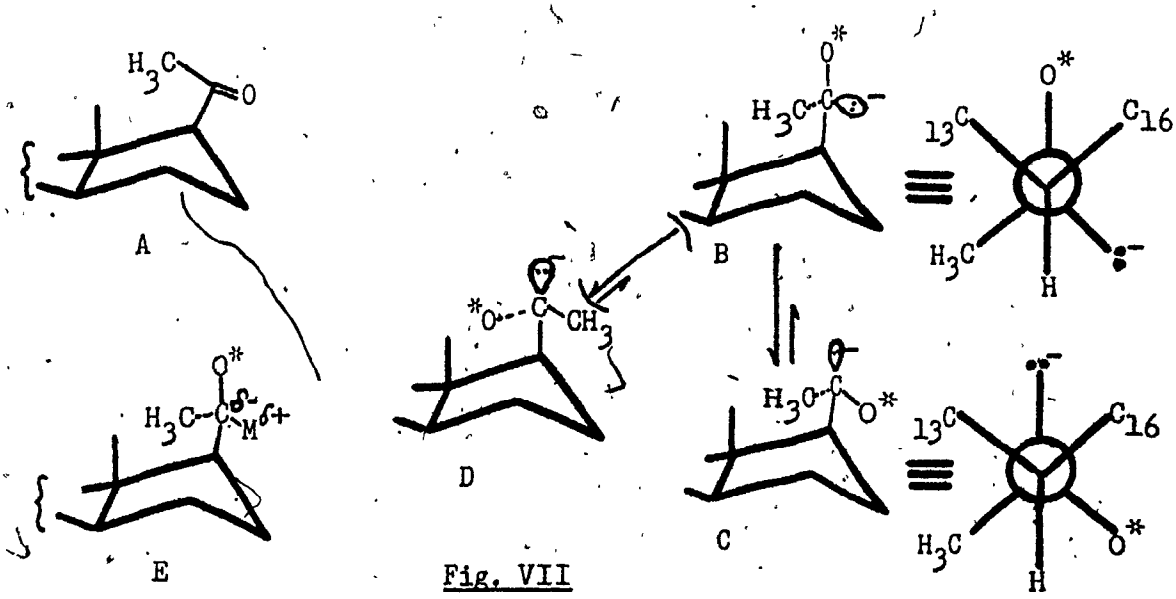


Fig. VII

is a C_{20}-carbanion unencumbered by a metal cation, protonation occurs**

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* The asterisk at oxygen expresses uncertainty as to whether this species should be represented as -OH, -O·, or $-O^-$, but this does not affect the argument concerning the stereochemistry at C_{20}.

** Since 20-ols do not epimerize significantly under normal conditions, the stereochemistry of the 20-ols is determined irreversibly at the moment of attachment of the proton at C_{20}.

before equilibrium* between B and C is attained. On the other hand the torsional strains about the C_{17}-C_{20} bond restrict the rotation needed for the side chain to attain the preferred rotomer D and it is assumed that the carbanion has the more stable configuration C yielding 20α-ol. Another mechanism which was suggested by Barton and Morrison[43] invokes the existence of transient C-metal bonding during the reduction process, such bonding occuring mainly on that side of C_{20} giving configuration E(Fig. VII). The protonolysis of the C-metal bond which is largely ionic** would be accompanied by inversion to give mainly the 20α-ol.

Steroidal ketones may also be reduced catalytically with hydrogen. The most useful catalysts are platinum and nickel. The mechanism of the reduction was explained in two distinct ways.[34] The side chain conformations of 20-keto steroids in the "half-reduced" state will differ depending upon whether a metal-oxygen or metal-carbon bond is involved. In non-acidic media the carbonyl group is considered to bond to the catalyst mainly through oxygen to form a complex represented by A(Fig. VIII), while in acidic media a protonated form Ea of the ketone is considered to bond to the catalyst by accepting electrons into the formally vacant p-orbital of the carbonium ion Eb to give C(Fig. VIII).

Due to the steric requirement that the metal surface in each case lie in the direction away from the main bulk of the steroid molecule, completion of each reduction by hydrogenolysis of the O-metal or C-metal bond would give products rich in the 20α- or 20β-ol, respectively.[35]

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* A low energy barrier to carbanion inversion is assumed by Barton.[35]

** The inversion reaction should occur more readily the more ionic the C-metal bond.

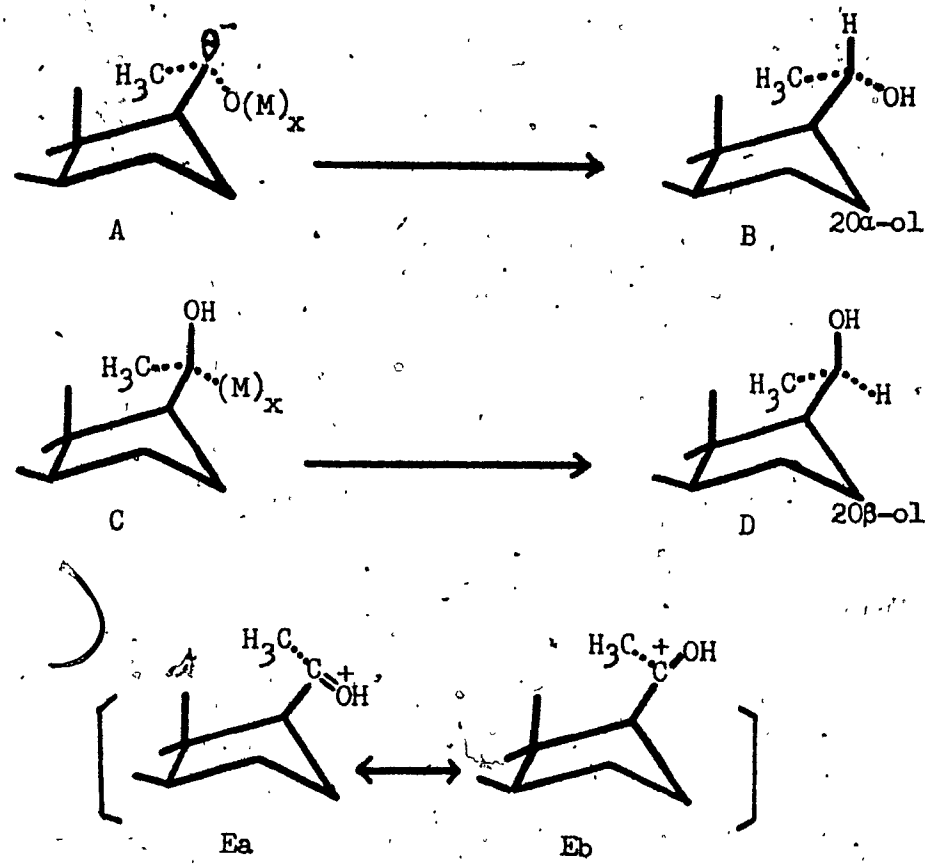
H3C
O(M)x
A
H
H3C
OH
20α-ol
B
OH
H3C
(M)x
C
OH
H3C
H
D
20β-ol
H3C
C
OH
Ea
H3C
C
OH
Eb

Fig. VIII

DISCUSSION

Preparation of 18-Oximino-20β-hydroxy-5α-pregnan-3-one(9).

J. Pospisek, et al.[4] fully reviewed the methods for preparation of 17β-hydroxy-5α-androstan-3-one(dihydrotestosterone) and outlined a new approach which was based on the well established observation that the 5,6-double bond in a steroid is hydrogenated stereospecifically forming predominantly 5α-dihydro derivatives(allo configuration).[48] This concept was further supported by the experiences of several workers[49,71] who investigated the stereochemistry of hydrogenation of 3,3-ethylene ketals in the Δ^5-cholestene series.

Cyclic ketals have proven to be versatile blocking groups[49] and the mechanism of the ketal formation is well understood.[50] Their formation may be restricted by steric factors and accompanied by rearrangement of the double bond of a Δ^4-3-ketosteroid to the C_5-C_6 position. R. Antonucci, et al.[44] presented evidence in support of the double bond rearrangement. Moreover, it has been pointed out that the negative rotatory power of the Δ^5-ketal may be considered as corroborative evidence for the assigned structure, agreeing with the result of the later work* of H. L. Herzog, et al.[51]

The mechanism of catalytic hydrogenation[52] involves: i) adsorption of hydrogen with the formation of a bond to the active centers on the catalyst surface, ii) at least partial dissociation of the H_2 molecule to give reactive hydrogen atoms bonded to the catalyst, iii) attachment

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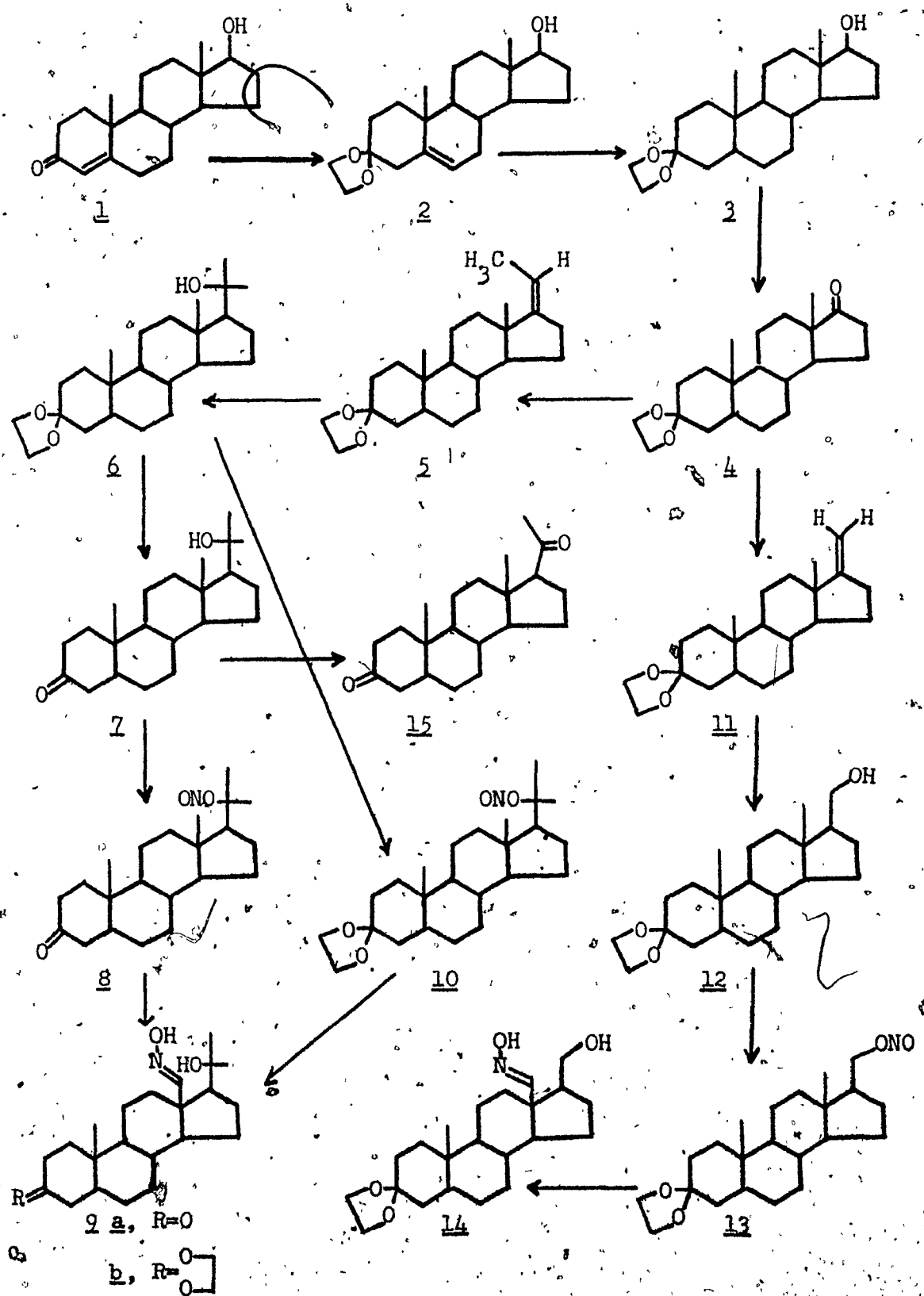
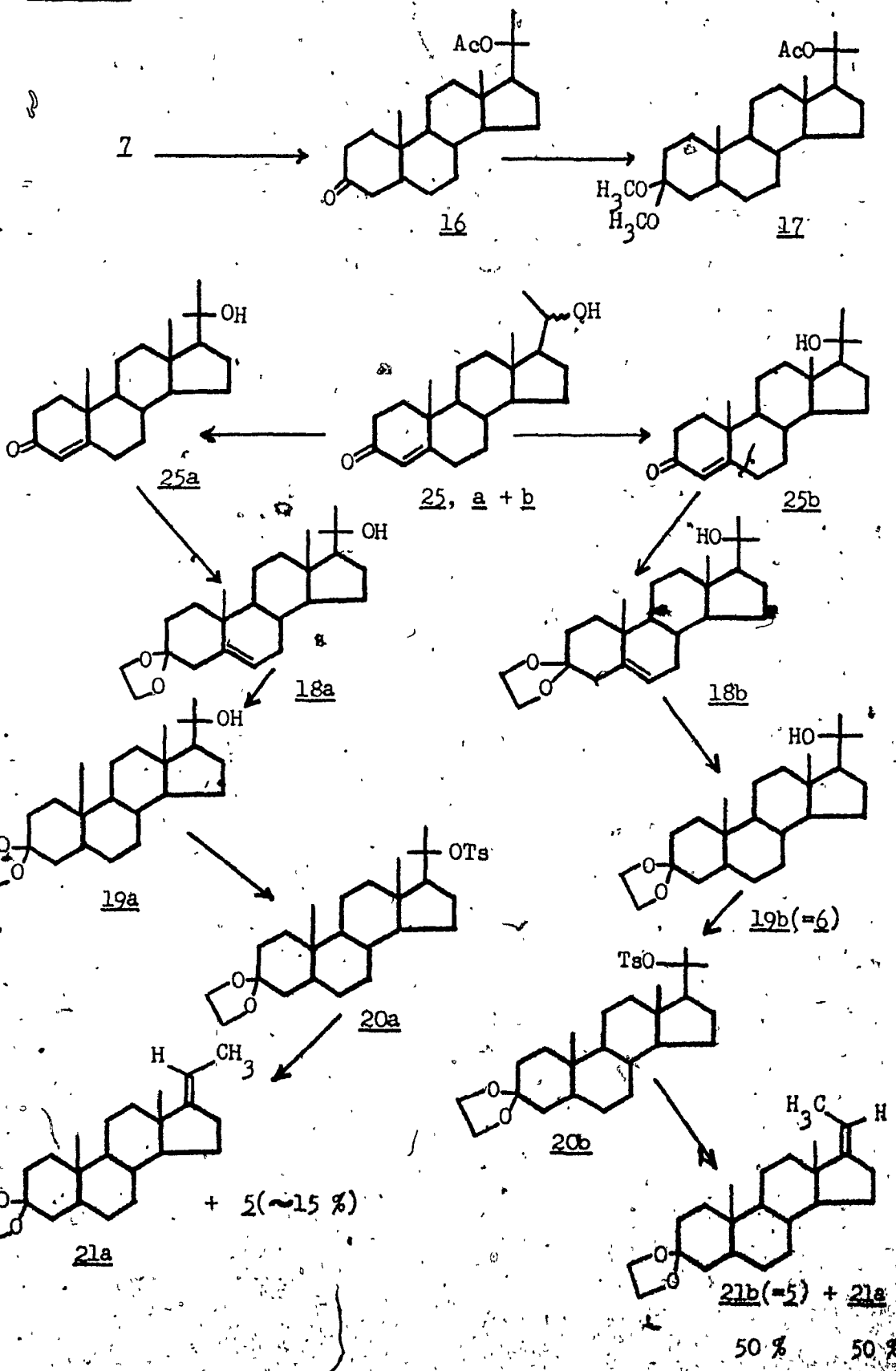
* An attempt was made to establish the course of oxathiolane and dioxolane formation in the 3-keto-Δ^4-system by the application of Barton's method[59] of molecular rotation differences.



Scheme 6

Scheme 6 continued.



of the olefin to adjacent active centers by two σ-type bonds formed by overlap of free carbon p-orbitals with the d-orbitals on the metal surface,[58] and iv) addition of two hydrogen atoms in discrete steps from the neighbouring catalyst surface with consequential cis addition

The ketalization of testosterone(1) does not proceed to completion even with continuous removal of the water as it is formed. Thin layer chromatography(TLC) shows that the ratio of the starting material to the ketal(1 : 7~10) is virtually unchanged after 3~4 hours. Hydrogenation of the 3-ketal 2 over 5 % Pd/C catalyst proceeds best with a steroid to catalyst ratio of 3 : 1 under high dilution conditions, since the product was considerably less soluble in the solvent than the starting compound. If the latter precaution is not observed the product may be deposited on the catalyst surface halting the reaction.

The double bond rearrangement(from Δ^4 to Δ^5) was determined by the negative rotatory power of the Δ^5-isomer(2) and the hydrogenated compound by optical rotatory dispersion(ORD) and NMR experiments. The positive Cotton effect of 20β-hydroxy-5α-pregnan-3-one(7) was contrasted by negative Cotton effect of 20β-hydroxy-5β-pregnan-3-one(30)(Fig. IX). The assignment of the 5α-configuration by NMR was elucidated by comparing spectra of the cyclic 3-(ethylene acetal)(6) and its 5β-isomer(31)(Table V on page 40).

The chromium trioxide-pyridine complex oxidation of an alcohol proceeds through rapid formation of a chromate ester followed by rate-controlling abstraction of the carbinol proton in an elimination process. Oxidation of a series of steroidal alcohols with this reagent reveals a markedly greater rate of oxidation for axial hydroxyl groups at each skeletal position, as well as a pronounced trend to faster

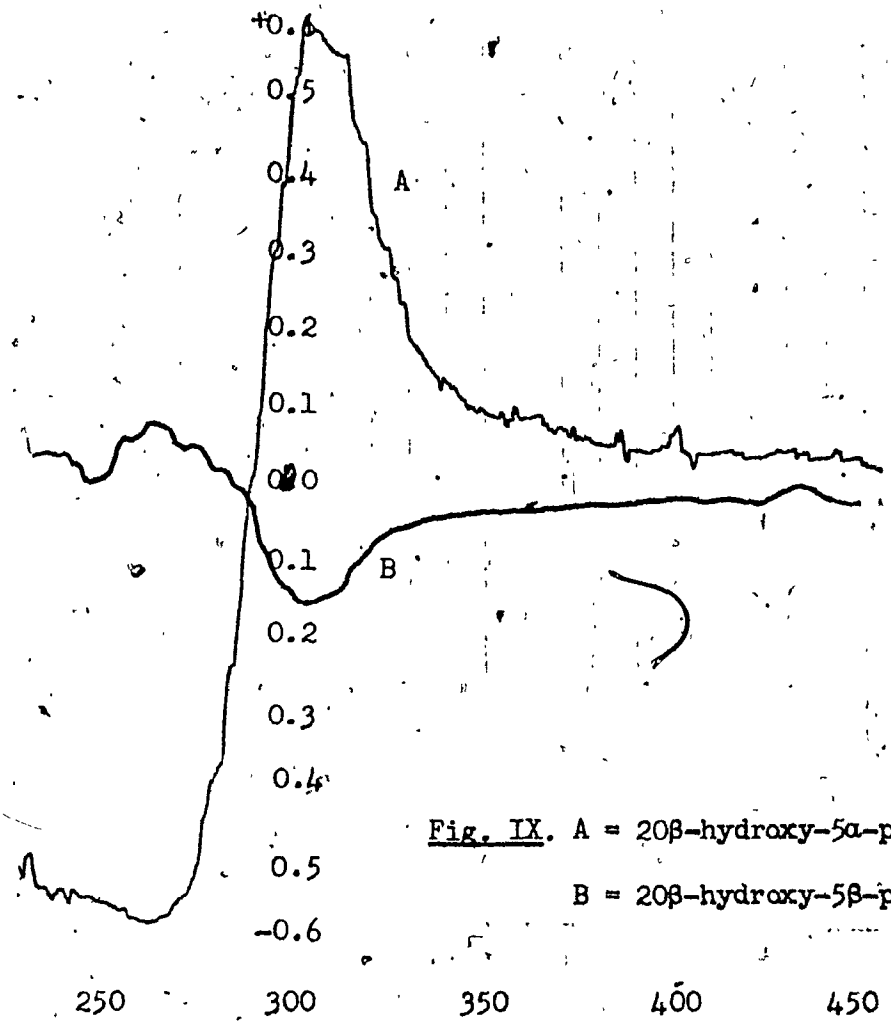


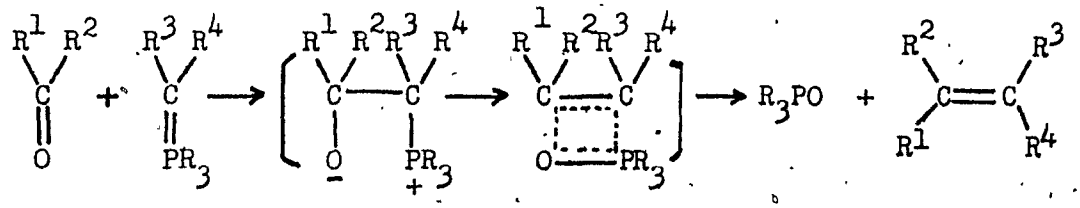
Fig. IX. A = 20β-hydroxy-5α-pregnan-3-one(7).
B = 20β-hydroxy-5β-pregnan-3-one(30).

reactions as the hydroxyl group becomes more sterically hindered. Schreiber and Eschenmoser[53] have suggested that this faster reaction is steric in origin. Any strain in an axial alcohol or its chromate ester, by virtue of interactions with syn-axial(1,3-diaxial non-bonded interactions) groups, is relieved in forming the corresponding ketone. This relief must be at least partially present in the transition state leading to the ketone, when the ring carbon is changing from an sp^3 to sp^2 hybridized state. Thus the activation energy is lower for a strained than an unstrained equatorial chromate ester.

The first reported use of the CrO_3-pyridine complex in pyridine solvent to oxidize alcohols was by G. I. Poos, et al.[60] and has since

seen widespread use in the steroid field. The advantages of the reagent are:[45] i) the reactivity of the chromium trioxide-pyridine complex in pyridine is lowered, so the reagent shows the desired inertness toward double bonds and thioethers, ii) the reaction medium is non-aqueous* and basic, so acid sensitive groups are not attacked by the reagent, and iii) the oxidation reaction can generally be carried out at room temperature. Since the 17β-hydroxyl group is in a somewhat hindered location, the oxidation(3 → 4) was accomplished in good yield, being essentially complete after 3 hours.

The Wittig olefin synthesis[54] involves the nucleophilic addition of an alkylidenephosphorane A(Scheme 7) to a carbonyl compound, followed by elimination of a phosphine oxide from the intermediate betaine B via a four-membered cyclic transition state C to give the olefin D.



A B C D

Scheme 7

Alkylidenephosphoranes are obtained under basic conditions by α-elimination of alkylphosphonium salts having at least one α-hydrogen. The strength of base necessary to effect elimination depends on the acidity of the hydrogen to be abstracted and may vary from aqueous sodium carbonate to amide-ions. Bases and solvents commonly employed

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* Primary alcohols are reported to give aldehydes in a non-aqueous medium.[75]

include butyl- and phenyl-lithium compounds in ether, benzene, or tetrahydrofuran and sodium, lithium, or potasium alkoxides in the appropriate alcohol, as well as dimethyl formamide or dimethyl sulfoxide. The use of dimethyl sulfoxide metalated by sodium hydride, i.e. $MeSOCH_2^- Na^+$(Methylsulfinyl carbanion), with dimethyl sulfoxide as solvent, has been described[55] and recently applied extensively to ylid chemistry.[56,57,61]

The stereochemistry of carbonyl olefination had generally been considered of little promise for the purposes of organic synthesis. However, Bergelson and Shemyakin[62] were able to control the stereochemistry of olefin formation by varying the reaction conditions and structure of the ylid. The presence of a sufficiently nucleophilic Lewis-base and a polar aprotic solvent promote cis-olefin formation. In the absence of Lewis bases and in non-polar media, dipole-dipole interactions and mutual repulsion of the substituents $R^{1\sim4}$(Scheme 7) on the reactants lead predominantly to trans olefins. On the other hand, phosphoranes with a carbonyl group attached to the α-carbon atom or with a sufficiently low positive charge on the phosphorus atom also give largely trans olefins.

Concepts of these types were applied to the reactions of a number of 17-keto steroids,[46,47,63] providing olefins in high yield and with high stereospecificity. The processes are exemplified by Scheme 7, where the phosphorane in dimethyl sulfoxide is present in 4 to 5 fold excess and the reaction mixture is maintained at 55-60° for more than 3 hours.[64]

The reaction between a 17-keto steroid and ethylidenetriphenyl-phosphorane gives predominantly cis-olefin. This geometry was

substantiated by experiments of House[65] and by hydroboration[46,63,66] and osmium tetroxide reactions.[72a,b] The formation of the cis-olefin* is believed to proceed by rate-determining nucleophilic attack of the phosphorane on the carbonyl group, forming a phosphonium betaine intermediate B(Fig. X). Rapid cis-elimination of triphenylphosphine oxide

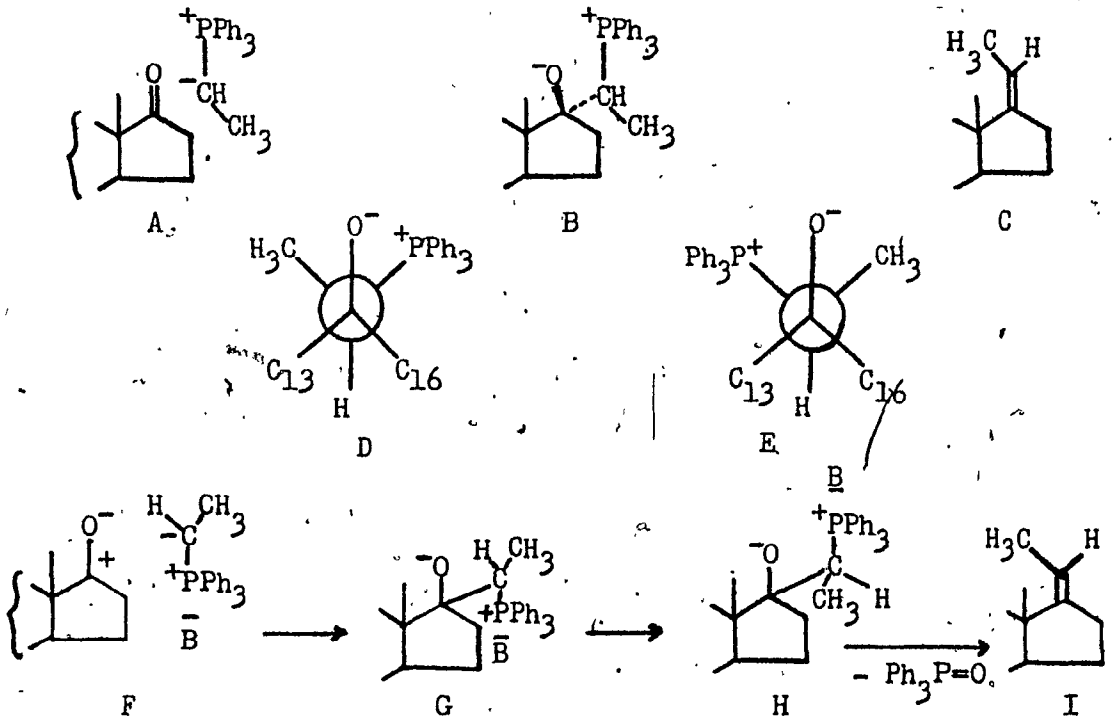

Fig. X

then leads to the olefinic product. An unsymmetrical ketone may give two diastereoisomeric betaines D and E(shown above in Newman projection) and

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* The designations, cis and trans, in these 17-ethylidene steroid compounds refer to the relative configurations about the 17(20)-double bond of the substituent at C_{20} and the C_{17}-C_{13} bond.[67] The designation E and Z(J. Org. Chem., 35, 2849(1970)) corresponds in this compound to trans and cis, respectively.

the less sterically crowded intermediate D is formed more rapidly, giving cis-olefin by cis-elimination.

Another explanation by other authors[47,62] having a somewhat different point of view in some aspects arrives at the same result. In Fig. X, F, the charged phosphorous atom interacts with Lewis base (B: or B^-)* and the solvated atom becomes less electrophilic so that a dipole-dipole interation will no longer exert a decisive influence on the orientation of the reactants. The stereochemistry of these solvated molecules is governed by steric factors in the betaines (Fig. X, F~H) and the reaction proceeds with formation of the cis-olefin.

The reaction of 5α-androstane-3,17-dione cyclic 3-(ethylene acetal) (4) with an excess of ethylidenetriphenylphosphorane in DMSO[55] at room temperature under nitrogen gave predominantly a single product. A second compound with a higher R_f value was detected as a very faint spot on the TLC plate, but the quantity was too small to permit isolation. NMR of the principal product showed methyl resonances at δ 0.83 and 0.87, while the starting material(4) had only single peak at δ 0.86 corresponding to the overlapping 18- and 19-methyl groups. The assignment of the geometry of ethylidene side chain has been effected by NMR in a number of cases[67,68,69] and it has been shown that, in

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* House[65] stated that his data are compatible with the idea that cis-isomer formation is enhanced by a proton donating solvent or Lewis acids, such as a lithium cation in solution, and are not consistent with the idea of prior coordination of the ylid with a Lewis base. He preferred to explain his results in terms of a coordination of the Lewis acid with the carbonyl oxygen.

contrast with the trans-ethylidene derivative, cis-$\Delta^{17(20)}$-enes deshield the 18-methyl group relative to its resonance frequency in the 17-ketone.* This deshielding is approximately 0.5 Hz for the cis-isomer, while a shielding of 7~8 Hz is observed for trans-isomer.[67a,69b] Other authors have also observed that a trans configuration about a C_{17}-C_{20} double bond provides a greater shielding effect on the 18-methyl protons than the corresponding cis-isomer by approximately 6-12 Hz(at 60 MHz). In our case it was ambiguous whether the shielded(2.0 Hz) or the deshielded(0.5 Hz) peak should be assigned as the 18- or 19-methyl group of the 5α-$\Delta^{17(20)}$-ene 5.

The cis- and trans-isomers were prepared from 20β-hydroxypregn-4-en-3-one(25b) and from the 20α-isomer(25a) respectively and the NMR data were compared with those of the product 5 to establish structure. The 20α-tosylate 20a was transformed to the trans-olefin 21a by a predominantly trans-elimination process[72a](with a small amount, 10-15 %, of the cis-olefin). However, the 20β-tosylate 20b gave equal amounts of cis- and trans-olefin(5 and 21a) upon treatment with base. The products formed in the latter process have been ascribed to a trans elimination producing the cis-Δ^{17}-olefin 5 and an E1 or E2 mechanism in an ionic cis elimination reaction[72a] producing trans-olefin 21a. The proton resonance peaks of 18- and 19-methyl groups of the trans-olefin 21a appeared at δ 0.73 and 0.83, respectively. The corresponding peaks of the cis and trans mixture derived from 20β-tosylate appeared at δ0.73, 0.83, and 0.87 with a ratio of peak heights of 1 : 2 : 1. Thus the peaks at δ0.83 and 0.87 of product 5 were assigned to the compound with the cis

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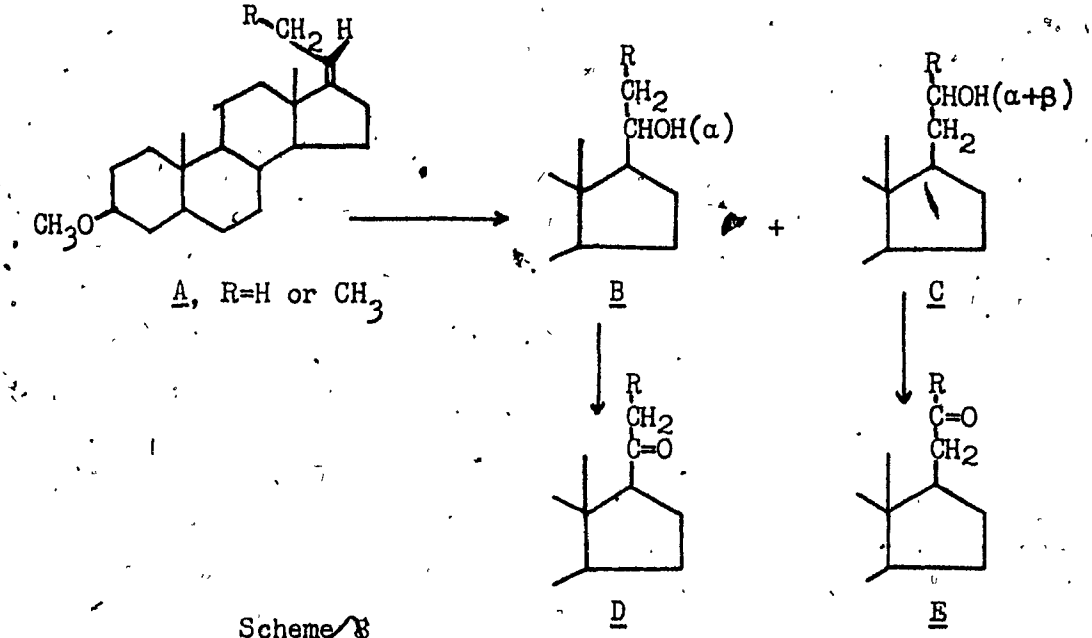
* A 17-keto and C_{17}-C_{20} doubly bonded compounds appear to lower the proton shift of the 18-methyl by 10-12 Hz(at 40 MHz).[70]

configuration.

The hydroboration method of converting a double bond to an alcohol takes place in two steps. Borane adds across the double bond such that the boron atom is generally attached to the less substituted center and the resulting alkylboranes are oxidized with hydrogen peroxide and dilute sodium hydroxide solution to alcohols. The latter reaction involves a migration of an alkyl group from boron to oxygen with retention of configuration.[83] The alcohol formation from olefin thus becomes an indirect way of adding H_2O across a double bond in an anti-Markovnikov manner. A number of reports of the applications of hydroboration of $\Delta^{17(20)}$-steroids to provide 20α-hydroxy compounds have appeared in the literature.[46,47,66] The addition process of the hydroboration reaction is stereoselectively cis, that is the attack takes place almost exclusively from the less hindered side of the molecule.

The possibility of organoborane isomerization exists when the reaction is conducted at an elevated temperature.[80] Initially, the lowest temperature reported for an isomerization was 50°.[73] However, there is a recent report of a room temperature organoborane isomerization in the work of Ourisson.[74] Investigation of the effect of temperature on the C_{20}/C_{21} oxygenation ratio(the ratio of D/E(R = CH_3), Scheme 8) in the hydroboration-oxidation of A(R = CH_3), confirms that an isomerization takes place at room temperature.[63] Further investigation showed that the reverse reaction between the olefin and an alkylborane was practically complete at 65°.

No boron migration to the end of the three-carbon chain was observed even at 160°. With A(R = H), however, 21-alcohol(Scheme 8, C, R = H) was formed by conducting the reaction at 65°, but at a much



Scheme

slower rate than for the case where R = CH_3.

The configuration of a 20α-ol obtained by the addition of diborane to the less hindered side of a cis-Δ^{17}-olefin can be assigned by NMR.[72c] The 21-methyl proton resonance frequencies of the 20α-epimers appear downfield relative to those of the 20β-epimers.[72c] Since the oxygen atom of the 20β-ol in its most stable conformation is nearer to the 18-methyl group than is the case for the 20α-ol (Fig. VI on p. 14), the 18-methyl resonance frequencies of 20β-epimers are subject to greater deshielding. Acetylated 20-ols reverse this relationship due to the shielding effect of the carbonyl function and the reduced deshielding effect of the hydroxyl oxygen atom in the 20β-epimers. Based on these argument it is assumed that the 17β side chain has the same conformation[39a] regardless of whether the functional group at C_{20} is hydroxyl or acetoxyl.

The nitrosyl group at C_{20} is reported to exert a shielding effect in the 20β-isomers, but a deshielding effect in the 20α-series.[72c] The differing effect from that of an acetyl group was reported as one to be

expected, since the nitrosyl group can assume both "cis" and "trans" forms.[72c]

The C_{20}-hydrogen atom is close to the 18-methyl group and is subject to similar environmental effects, leading to shielding or deshielding. Lee, et al.[39a] determined the 17β side chain conformation of 20α- and 20β-oxygenated compounds by measuring the coupling constant between the 17α-hydrogen and the C_{20}-hydrogen atoms. It was shown that the magnitude of the coupling constant is not affected by the nature of the groups at C_{13} or by acylation of the hydroxyl group. By means of the Karplus equation,[81] the fully staggered conformation was assigned to the 20β-hydroxy compounds and the conformation intermediate between staggered and eclipsed, to the 20α-epimers. Therefore, in principle if the $J_{17\alpha\text{-H},20\text{-H}}$ can be determined, the configuration of C_{20}-substituent can be assigned.

The C_{20}-configuration can be assigned also by the "Method of molecular rotation differences."[82] In proceeding from the free 20-hydroxy steroids to the acetates, an increment in the molecular rotation is observed in one of the configurational series(20β-ol), while in the epimeric series a decrement is found.[72a,76,79]

Addition of diborane and H_2O_2 to the THF solution of Δ^{17}-olefin 5 were highly exothermic processes, so the temperature was controlled in a dry ice-CCl_4 bath employing vigorous stirring. The diborane addition process was maintained at room temperature, while decomposition of the alkyl borane was carried out < 0°. Under these conditions, a single product predominated to the extent of more than 90 % and pure alcohol 6 could be obtained by a recrystalization. If the temperature was not carefully controlled, various non-identified products were obtained.

The configuration of the hydroxyl group at C_{20} of the product 6 was assigned as the 20β, contrary to that expected. The configuration of C_{17} was assigned as beta, since the photolysis of the nitrite ester of 7 gave the 18-oximino derivative 9a, the reaction would have failed had the stereochemistry of the sidechain at C_{17} been alpha, and 5α-pregnane-3,20-dione(15) derived by oxydation of the 20-ol 7 showed NMR data corresponding to the calculated value(Table II).[99,100] NMR data of 20-

Table II. Calculated* and Observed(in Parentheses) Angular Methyl Groups Chemical Shifts of 5α-Pregnane-3,20-dione(15) and Its 17α-isomer.

Isomer	18-CH_3	19-CH_3
17α[100]	56.4	61.2
17β[100]	37.8	61.2
17β[99]	39.0(39.0)	61.5(61.0)

* Appendix I

hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(6) prepared from the Δ^{17}-olefin 5 were compared with those of 20α-(19a) and 20β-hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(19b) prepared from 20α-(25a) and 20β-hydroxy-4-pregnen-3-one(25b), respectively(Table III). The 18- and 21-methyl resonances of the 20α-hydroxy compound 19a were observed at δ0.66 and 1.20(doublet, J=6.0 Hz), respectively. The 18-methyl absorption of the 20β-hydroxy compound 19b is at lower field than of the 20α-isomer 19a, while the 21-methyl group appears at higher field, a characteristic phenomenon of epimeric 20-ol steroids.[72c] The NMR data of 20-hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(6) were in

good agreement with those for the 20β-hydroxy compound 19b and those for the deketalized compound 7 also corresponded to the calculated values for a 20β-ol(Table III). The beta configuration at C_{20} of

Table III. Calculated* and Observed(in Parentheses) Angular Methyl Groups Chemical Shifts of 20-Hydroxy-5α-pregnan-3-one and Its Derivatives.

Compound	18-CH_3	19-CH_3
20β-hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(6)	44.0(45.0)	49.0(49.2)
20β-hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(19b)	44.0(45.0)	49.0(49.0)
20α-hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(19a)	38.5(39.8)	49.0(48.8)
20β-hydroxy-5α-pregnan-3-one(7)	46.5(47.0)	61.5(61.2)
20α-isomer of 7	41.0(-)	61.5(-)
10(nitrite ester of 6)	- (38.0)	- (46.8)
16(20β-acetate of 7)	39.0(38.8)	61.5(59.5)
20α-isomer of 16	42.0(-)	61.5(-)

*Appendix I

the hydroxy steroids, 6 or 7, was further supported by its melting point and the direction of the shifts of the 18-methyl group resonance frequencies of the 20-acetate 16 and the 20-nitrite ester 10(Table III). The upfield shift of the former(16) by 8.2 Hz and of the latter(10) by 7.0 Hz relative to the 20-ol(7 and 6, respectively) were in accordance with previous predictions.[72c]

The configuration of the final alcohol 6 or 7 could a priori be explained on the basis of the olefin 5 having the trans-configuration,

instead of cis as has been reported for the product of this type of Wittig reaction of 17-keto steroids. However, it has been shown(see above) that the olefin configuration is definitely cis and we must therefore conclude that an inversion has taken place during the hydroboration-oxidation process. No precedent exists for inversion of alkylboranes with H_2O_2 under basic conditions and therefore further investigation would be necessary in order to clarify the mechanism in this respect.

The Wittig reaction of the 17-keto compound 4 with methylenetriphenylphosphorane gave 17-methylene-5α-androstan-3-one cyclic 3-(ethylene acetal)(11): NMR chemical shifts showed both 18- and 19-methyl groups were shielded by 4.0 and 2.0 Hz, respectively, relative to the starting material. The C_{20}-vinyl protons appeared as an ill-defined multiplet. The hydroboration product 12 had an 18-methyl peak at δ0.65, almost identical in position with the one for 20α-hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(19a)(δ0.66). The 18-methyl proton resonance appears in the region close to that expected for the conformation of the 17β-hydroxymethyl compound 12. In Fig. VI(p 14) the most stable conformation of 12 will have the hydroxyl group in a position close to that for the most stable conformation of the 20α-hydroxy compound. However, the 17β-hydroxylmethyl compound 12 will exist in a fully staggered form about the C_{17}-C_{20} bond because of the absence of a non-bonded interaction between the 21-methyl group and the methylene group at C_{12}. The 20-nitrite ester 13 of the alcohol 12 also showed the typical behavior of alpha series nitrite esters, namely to deshield the 18-methyl group by 3.0 Hz relative to the free alcohol 12.

Preparation of 18-Oximino-20-hydroxypregn-4-en-3-one(27) and 18-Oximino-20β-hydroxy-5β-pregnan-3-one cyclic 3-(ethylene acetal)(33b).

Enamine derivatives of steroidal ketones have found use as protecting groups and have been proven stable to concentrated acids. Enamine formation involves addition of a secondary amine to the carbonyl group to give a carbinolamine intermediate which then loses a molecule of water. The pyrrolidinylenamines of Δ^4-3-keto steroids were inferred to be 3,5-dienes rather than the alternative 2,4-dienes, primarily on the basis of their strong levorotation.[84] Further evidence based on molecular rotation studies have established the presence of a hetero-annular diene system in a neutral solvent.[78] In ethereal solution the enamine exhibited an ultraviolet absorption maximum in the 280-284 nm* range, while the expected UV maximum of a cross-conjugated steroidal 3-amino-2,4-diene is 278 nm. It is therefore not possible to distinguish between the two isomeric dienes on the basis of the UV absorption maximum. However, upon consideration of molar extinction coefficients(transoid dienes give a value of ϵ = 14,000-28,000, while those of cisoid dienes fall into the region of 5,000-15,000), a distinction between the two isomers can be made.[85]

The selectivity in the protection of ketone-functions of polycarbonyl steroids can be achieved by a suitable choice of amine.[87] As observed by Heyl and Herr[84] the 20-keto function of progesterone(22) failed to react with pyrrolidine. However, the Δ^4-3-keto group of 22 reacted

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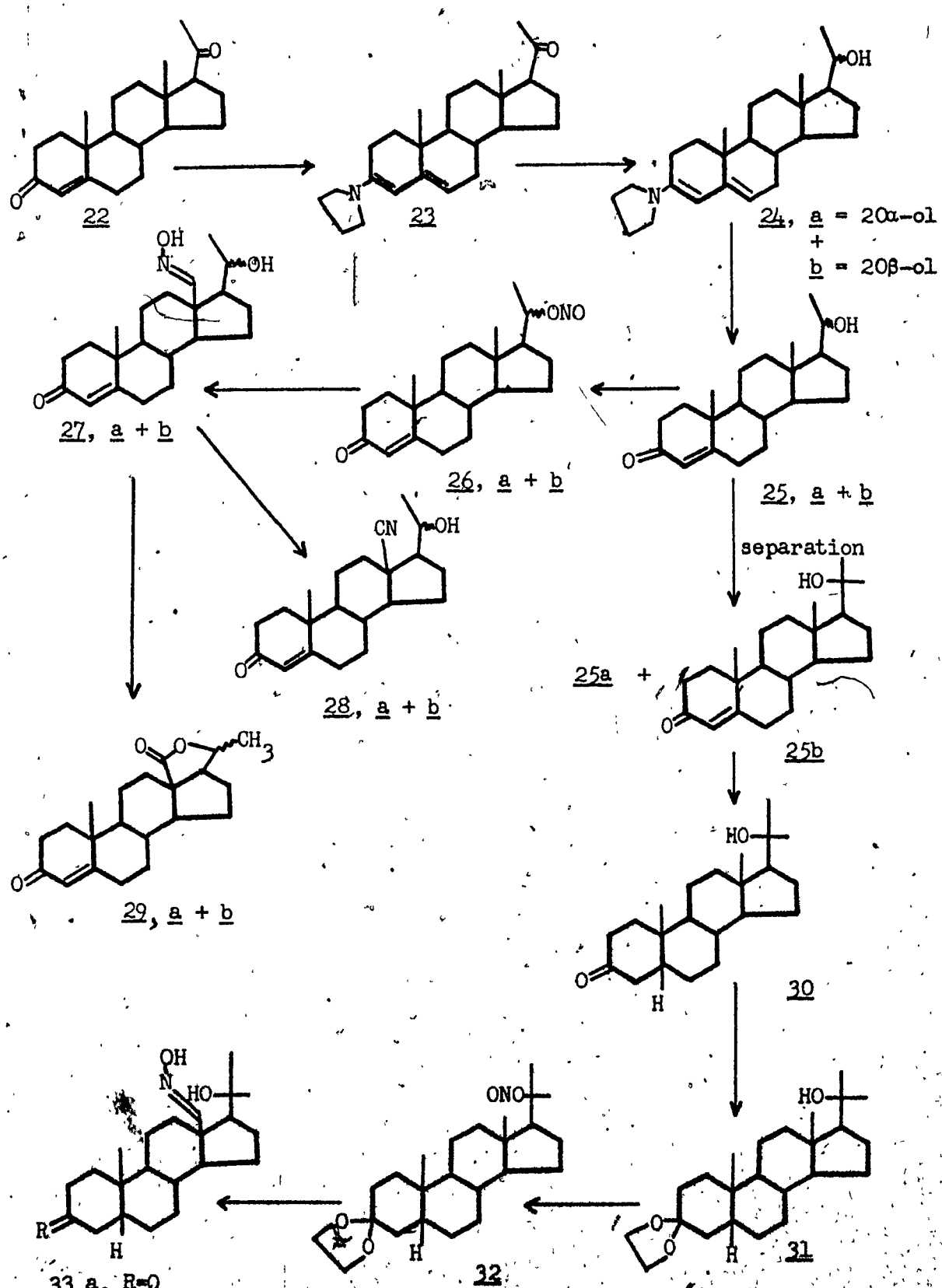
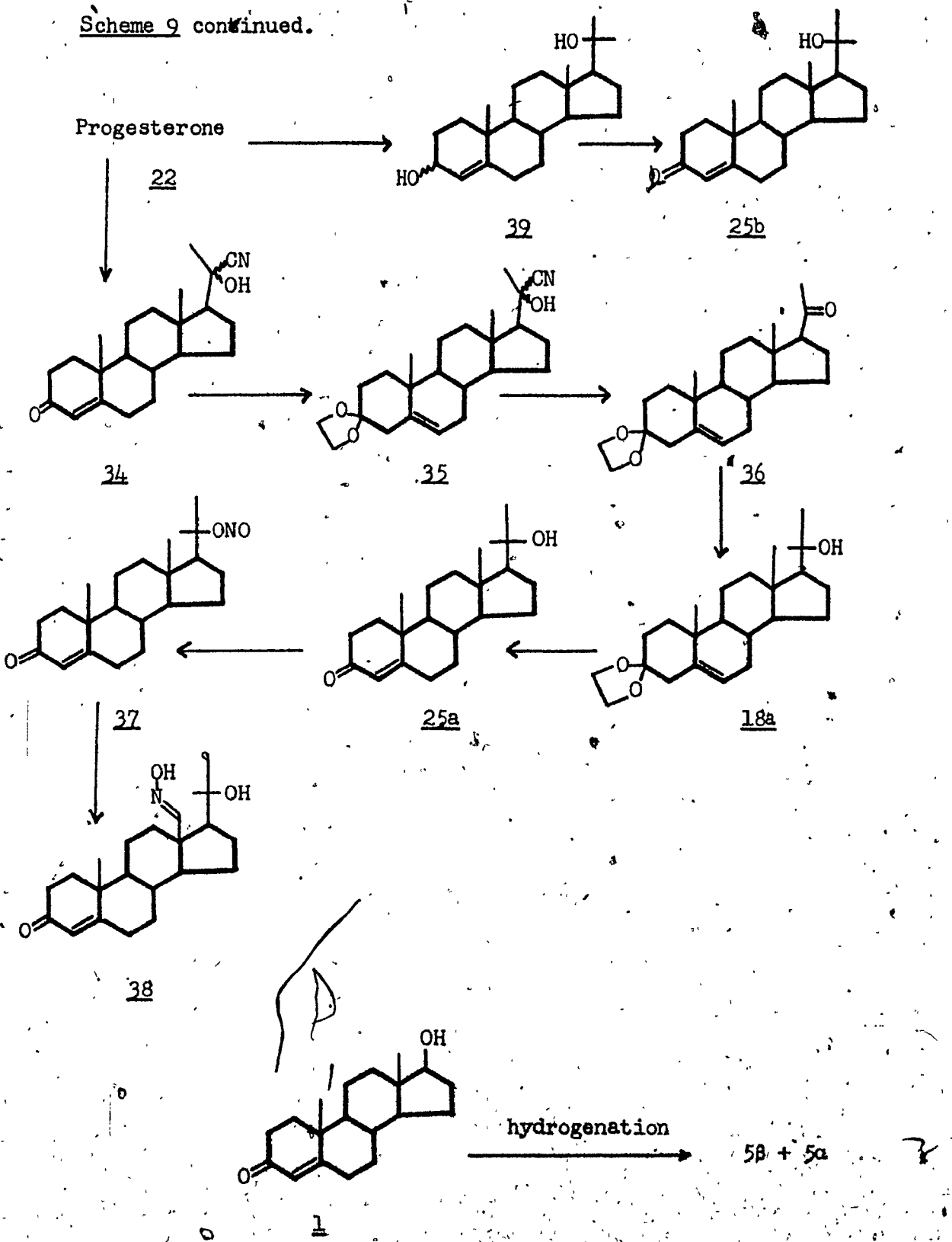
* Conjugation of simple conjugated systems with a tertiary amine function led to bathochromic shift somewhat larger than those obtained by conjugation with an additional double bond.[86]


22
23
24, a = 20α-ol + b = 20β-ol
25, a + b
separation
25a + 25b
26, a + b
27, a + b
28, a + b
29, a + b
30
31
32
33 a, R=O
b, R=O,O

Scheme 9

Scheme 9 continued.



spontaneously with the amine in warm methanol to give almost a quantitative yield of enamine.

LAH reduction of the unprotected 20-keto group of progesterone 3-pyrrolidinylenamine gave a mixture of 20α- and 20β-ols in the ratio of 4 : 5, the reaction showing very little stereoselectivity. Generally, however, steroidal 20-keto group reductions with LAH give predominately 20β-ols. The enamines are readily hydrolysed by basic or dilute acidic media.

Photolysis of the 20-nitrite esters of the mixed 20α- and 20β-ols (25a,b) led to 18-oximino-20-hydroxyprogesterones(27a,b) with a maximum yield of ~32 %. The oximes were simultaneously acetylated on both hydroxyl groups and treated with base to give the epimeric nitriles 28. The low yield of the 20α- and 20β-hydroxynitrile mixture was attributed to the differing reaction conditions required to prepare pure 20α- and 20β-isomers. On the other hand, treatment of the mixture of oximes (27a,b) with $Na_2Cr_2O_7$ in acetic acid solution produced a better yield (78.4 %) of the 20-hydroxy-4-pregnen-18-oic acid 18,20-lactone(29a,b) than has been reported for the separated pure isomers.[15d]

Separation of the 20α- and 20β-ols(25; a and b) encountered difficulties because of the similar polarities of the alcohols. Generally, repeated chromatography has been reported to be necessary for an acceptable separation and yield. Thus, Nathan and Marlatt[88] reported that for the separation of 28 g of 25, 34 l of solvent were required for elution employing a Florisil packed column. These workers rechromatographed fractions containing the 20α-hydroxy steroid(25a) in less than 95 % purity. In our hands, however, a trial separation of the mixture employing dry column chromatography[89] proved to be more efficient.

Using this technique, 51.3 % of the 20β-ol, 24.0 % of the mixture, and 22.6 % of the 20α-ol were obtained after a single pass through a deactivated alumina column. The dry column technique offers an additional advantage of requiring much lower quantities of eluting solvent. Confirmation that the system, alumina-$CHCl_3$, gives an effective separation of the isomeric alcohols was obtained by TLC.

The hydrogenation of a Δ^5-3-ketal steroid takes place on the less hindered α-face, while the stereochemistry of the reduction of a Δ^4-3-ketone shows a sensitivity to reaction conditions and also to remote structural features. Extrapolating from Siegel's model of the adsorbed cyclohexene molecule,[92] ring A will have a boat-like structure with an sp^3-hybridized carbon at C_4 and C_5 in order to form parallel bonds to the catalyst surface and the β-oriented carbon-catalyst model is considered to involve fewer non-bonded interactions between axial hydrogens and the catalyst surface. However, the hydrogenation of Δ^4-3-ketones generally yields a mixture of 5α- and 5β-compounds in various ratios, while hydrogenation in the presence of polar hydroxylic solvents[90] and solvents containing alkali or trivalent nitrogen groups[90,91] yields predominately 5β-compounds. The effect of alkali may be ascribed to the formation of enolate anions which are subsequently selectively reduced. The base-catalysed enolization is believed to give a $\Delta^{2,4}$-dienolate anion[93] which is seen from a molecular model to have an A/B ring system in a somewhat folded conformation(Fig. XI). Thus the approach of the

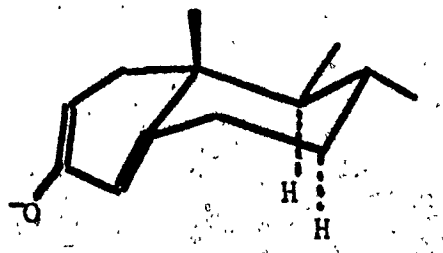


Fig. XI

catalyst to the convex β-face of the A/B ring system having no axial 2β-proton is favoured, while the α-face is hindered by the axial hydrogens at C_7 and C_9. In accordance with these observations, hydrogenation of 20β-hydroxy-4-pregnen-3-one(25b) in alcoholic-KOH solution gave the 5β-dihydro-compound 30.

The catalytic reduction[91] of testosterone(1) was also attempted under various conditions(Table IV). TLC confirmed that the 5β-compound was produced mostly when KOH was used as the base.

Table IV. Reduction of Testosterone.*

Conditions	Starting material (recovered)	: 5α	: 5β
1) EtOH-KOH soln., Pd black, > 2.5 h		1	20
2) EtOH-KOH soln., 5 % Pd/C, 3 h		1	20
3) EtOH-KOH soln., 10 % Pd/C, 3 h		1	20
4) EtOH-Et_3N soln., Pd black, 3 h		1	3~4
5) EtOH-Et_3N soln., 5 % Pd/C, 2.5 h		1	2
6) EtOH-KOH soln., Pd black, 45 lb. H_2 press., shaking for 2 h.		No reaction.	
7) EtOH-KOH soln., Pd black, 60 lb. H_2 press., shaking for 21 h.	1	1	5~10

* All reductions were carried out with 5 mg of testosterone under atmosphoric hydrogen pressure unless stated otherwise.

Hydrogenation of 11α-acetoxyprogesterone(41) was reported to give a 5β-derivative(59 %) in the presence of KOH in dioxane.[94] In our hands it was observed that if triethyl amine in ethanol was substituted for KOH-EtOH, the yield of 5β-reduced compound 42 could be improved to 87 %.

The presence of an 11α-hydroxy substituent will inhibit the formation of the intermediate formed when the catalyst approaches from the α-face of the molecule.

The 5β-configuration of the hydrogenated product 30 of 20β-hydroxy-4-pregnen-3-one(25b) was assigned on the basis of its negative Cotton effect and NMR.

The ketalization of the 3-keto compound 30 was carried out according to the previously described procedure, yielding 83 % of the desired product 31. With this ketalized compound the beta configuration at C_5 of the hydrogenated product 30 could be confirmed by observation of the chemical shift of the 19-methyl group. In agreement with a previous report[95] comparison of the NMR spectra of 5α- and 5β-3-ones and their ethylene ketals confirmed that the 3-keto compounds have almost the same spectra, while the derived ketals exhibit significant differences. The 19-methyl groups of 5α- and 5β-3-ethylene ketals were shielded with more profound shielding in the 5α-compound 6(5α, 12 Hz and 5β, 3.8 Hz) relative to the ketones(Table V) from which they were obtained.

Table V. Calculated and Observed(in Parentheses) Angular Methyl Group Chemical Shifts and $\Delta W_{h/2}$ for 19-methyl Groups of 20β-Hydroxy-5α-pregnan-3-one and Its 5β-isomer, and their ketal derivatives.

Compound	18-CH_3	19-CH_3	$\Delta W_{h/2}$
20β-Hydroxy-5β-pregnan-3-one(30)	46.5(46.8)	62.0(61.6)	0.4
5α-isomer(7) of 30	46.5(47.0)	61.5(61.2)	1.0
3-Ethylenedioxy ketal(31) of 30	44.0(44.9)	57.0(57.8)	
5α-isomer(6) of 31	44.0(45.0)	49.0(49.2)	

The stereochemistry of the A/B-ring junction can also be assigned by resorting to the well documented dependency of the peak width at half-height($W_{h/2}$) of the 19-methyl group, on the nature of the ring fusion. The long-range coupling constant for two protons separated by four saturated bonds is dependent on the dihedral angle between them. The largest coupling constants are observed in the systems which adopt the extended zigzag conformation, the coplanar "M" or "W."[96] In a trans fused A/B-ring junction(5α), three axial protons(1α, 5α, and 9α) can adopt this conformation with respect to the 19-methyl group(for ϕ_1' equal to 180°, the long-range coupling constant has values between + 0.4 and + 0.8 Hz), whereas in cis-fused(5β) compounds only one ring proton (9α) can be trans and the other three protons(1α, 1β, and 5β) are disposed at ϕ_1' equal to 60°(for gauche interactions of this type, methyl proton coupling constants ranging from 0 to -0.2 Hz have been observed) (Fig. XII).[97] Therefore, the peak width at half-height for the trans-

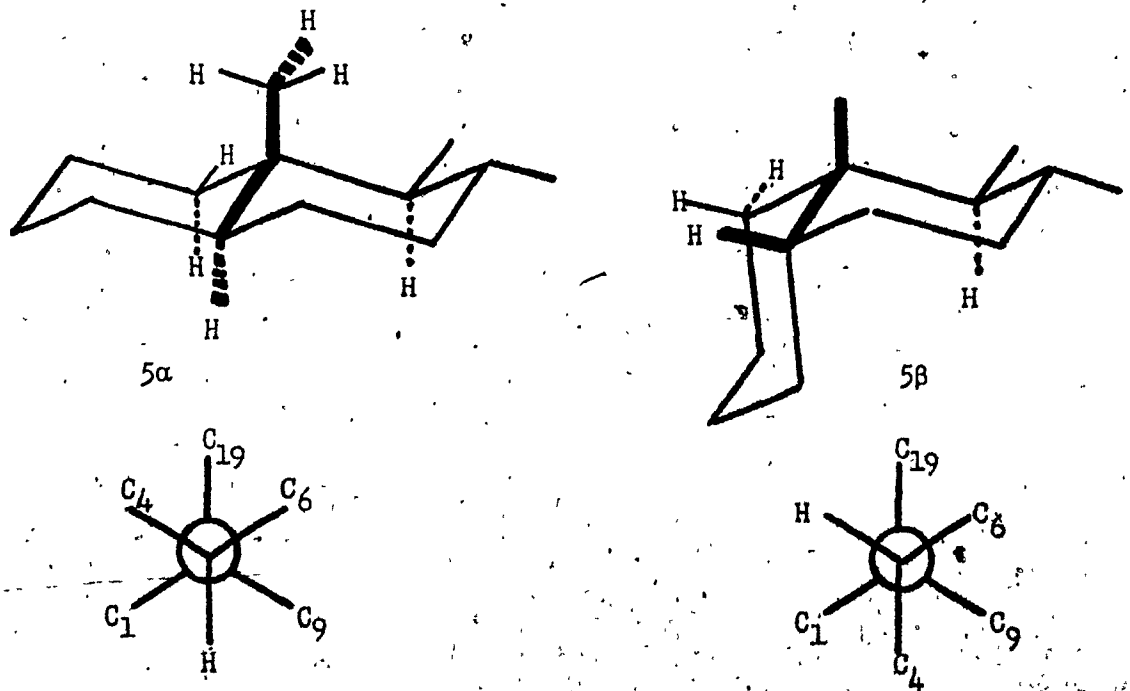


Fig. XII

fused(5α) isomer is always larger than that for the cis-fused(5β) isomer.[95,98] In accord with the above, the $W_{h/2}$ of the 19-methyl group less $W_{h/2}$ of the tetramethylsilane signal($\Delta W_{h/2}$) gave a value of 1.0 Hz for 20β-hydroxy-5α-pregnan-3-one(7) and 0.4 Hz for the 5β-isomer 30 (Table V).

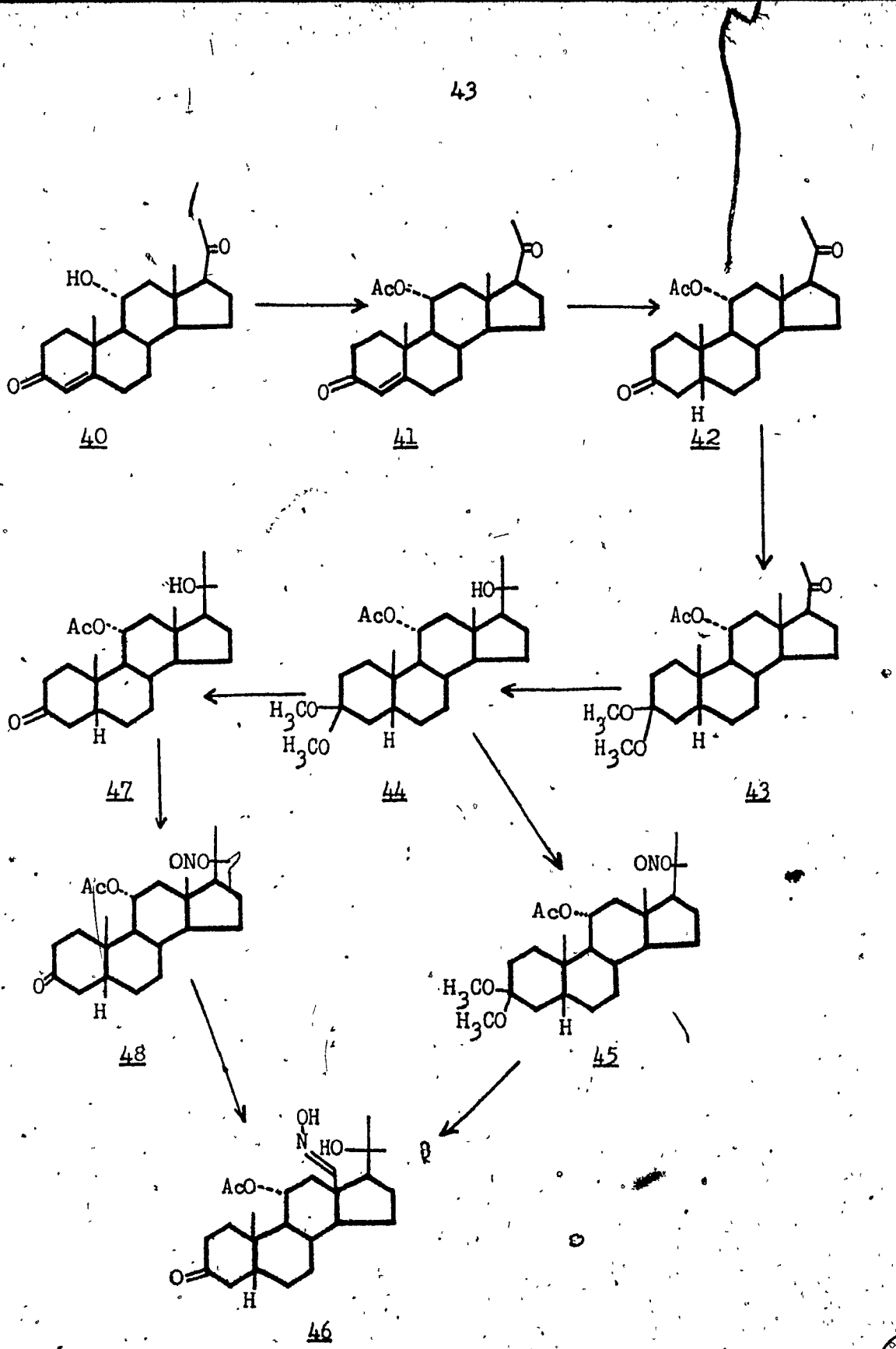
The 20β-ol 31 was treated with NOCl, yielding nitrite ester 32 in 82.9 % yield. The 18-methyl group of the nitrite ester 32 was shielded by 5.0 Hz with respect to the 18-methyl group of the 20-ol 31 as expected of the 20β-configuration.

The 20α-hydroxypregn-4-en-3-one(25a) and its 20β-isomer(25b) were also prepared in another fashion. The former was prepared by sodium reduction of the 20-keto compound 36 having a protected 3-keto group. Although the yield was low(overall yield based on progesterone(22) was only 18 %), this reduction gave 20α-ol as predicted by the mechanism. The 20β-ol was prepared by sodium borohydride reduction of progesterone and subsequent oxidation with manganese dioxide of the allylic alcohols of the reduction product. NMR spectra of the epimeric pair of 20-ols showed that the 18-methyl resonance of the 20β-hydroxy isomer appeared downfield from that of the 20α-epimer as expected.[72c]

Preparation of 18-Oximino-11α,20β-dihydroxy-5β-pregnan-3-one 11-acetate (46).

The acetylation of 11α-hydroxy progesterone(40) gave 11α-acetoxy progesterone(41) in almost quantitative yield. Subsequent hydrogenation of the ester was conducted in the presence of triethyl amine in order to prevent ester hydrolysis.

Selective protection of the carbonyl group at C_3 was accomplished



40 41 42 43 44 47 48 45 46

Scheme 10

by an extended reflux of the hydrogenated product 3,20-dione 42 in methanol in the presence of p-toluenesulfonic acid. The rate-determining step of the ketal formation is associated with the carbonyl carbon hybridization change from sp^2 to sp^3 and the hemi-ketal formation appears to be particularly sensitive to steric and conformational interference.[101] The formation of the dimethyl ketal of 5α-3-keto steroids is complete within several minutes,[102] while in the case of the 5β-steroid the reaction is slower.[90] The failure of dimethyl ketal formation at C_{20} also suggests that the rate-determining step is the formation of a sterically-overcrowded C_{20}-hemi-ketal intermediate.[103] It has also been reported that the selective protection of the 3-keto group is due to the fact that only the hemi-ketal at C_3 is more stable than the ketone.[101]

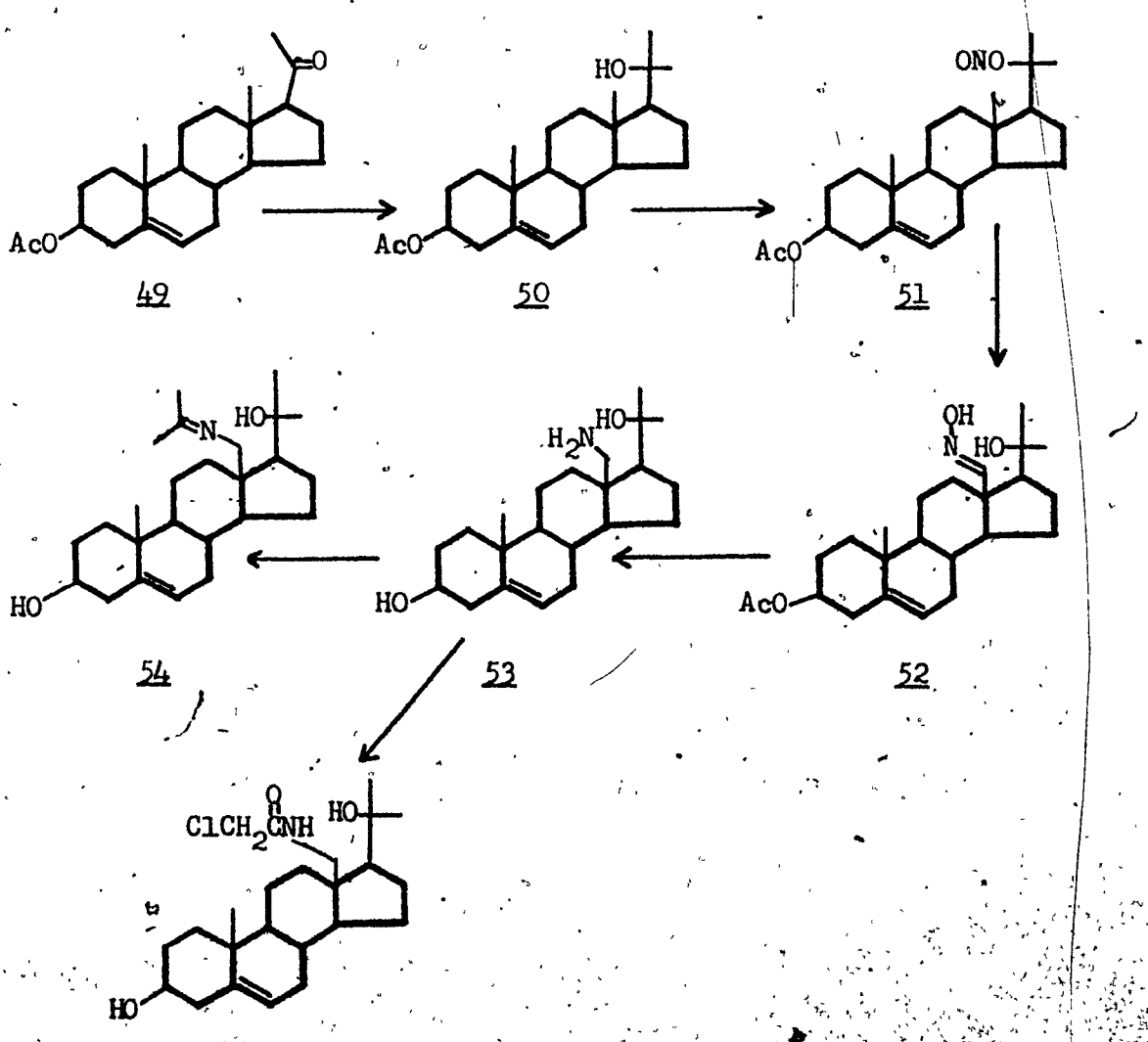
Sodium borohydride reduction of the 20-ketone 43 gave almost exclusively 20β-ol 44. The observed and calculated values of chemical shifts of 18- and 19-methyl groups of the 20β-hydroxy-3-keto steroid 47 and its 3-ketal derivative 44(Table VI), were in excellent agreement. Furthermore, the 18-methyl resonance peak of the nitrite ester 48 was shielded by 5.0 Hz with respect to the free alcohol 47 as expected in 20-ols having the β-configuration.[72c]

Table VI. Calculated and Observed(in Parentheses) Angular Methyl Groups Chemical Shifts of 11α,20β-Dihydroxy-5β-pregnan-3-one 11-acetate(47) and Its 3-dimethyl ketal(44).

Compound	18-CH_3	19-CH_3
47	50.0(49.0)	67.5(67.4)
44	47.5(47.3)	62.5(62.7)

18-Oximinopregn-5-ene-3β,20β-diol 3-acetate(52).

The reduction of 3β-acetoxypregn-5-en-20-one(49) with sodium borohydride was carried out in methanol either at room or at ice-bath temperatures. The ratio of the 20α- and 20β-ols(1 : 7~8) did not seem to vary with the reaction temperature. However, if the reaction mixture was stirred for several hours, considerable de-esterification occurred. The 3β-acetoxypregn-5-en-20β-ol(50), sufficiently pure for the purposes of the next reaction, was separated by one recrystallization from



49 50 51 52 53 54 55

Scheme 11

methanol in 77.7 % yield. The 20β-configuration was assinged on the basis of melting point, TLC(the less polar β-isomer has a higher R_f value than 20α-isomer), and NMR.

For the preparation of the nitrite ester of the 20-ol 50, the alcohol was suspended in pyridine and the cooled suspension was treated with nitrosyl chloride. When saturation of the pyridine suspension with nitrosyl chloride was complete the cooling bath was removed and the reaction mixture became homogeneous. The 20β-nitrite ester was readily isolated upon addition of water to the reaction medium. The 18-methyl resonance signal was shielded by approximately 5 Hz compared to the methyl signal in the 20β-ol.

The photolysis of the nitrite ester 51 gave principally nitroso dimer and a small amount of oxime. The dimer converted to the oxime during chromatographic purification; however, the transformation did not appear to be complete and the separation of oxime was difficult. The reaction mixture was therefore refluxed, prior to chromatography, with isopropyl alcohol in order to transform the dimer to the oxime 52.

The 18-aminopregn-5-ene-3β,20β-diol(53) was prepared by LAH reduction of the oxime(52) in dioxane. The isopropylidene derivative 54 of the amine was effected by warming with acetone. That imine formation had taken place was confirmed by the presence of an band at 1668 cm^{-1} (C=N stretching) and by the appearance of two peaks in the NMR spectrum at δ1.87(3H) and 2.04(3H), indicative of olefinic-type methyl groups. Reconverting the imine 54 to the amine 53 was readily performed in aqueous acetone solution containing a few drops of hydrochloric acid.

Chloroacetylation of the amine using α-chloroacetyl chloride could be carried out either in chloroform-pyridine or in chloroform-10 % NaOH

solution at low temperature. The chloroacetylation could also be accomplished with chloroacetic anhydride in methanol at room temperature. The heterogeneous Schotten-Baumann technique[104] gave a better yield than the homogeneous reaction employing pyridine as a base. Both reactions at 0° C caused no esterification of the alcohol functions. However, the chloroacetylation employing chloroacetic acid anhydride gave the amide and two other products as determined by TLC, possibly esterfication products of the hydroxyl groups. The yield of amide obtained by this technique was poorer than the heterogeneous Schotten-Baumann process. Ethyl monochloroacetate also offers possibilities as an acylating agent, but was not exploited for this work.

Summary of Results of Photolyses Experiments.

The wave length required for the efficient photolytic cleavage of nitrite esters is in the 320 to 380 nm region.[22,28] The absorption bands of nitrite esters comprise a low-intensity transition with six or seven superimposed vibrational fine-structure bands($\epsilon \sim 80$)(Fig. XIII).[22,28] A high pressure mercury 200 watt arc lamp(Hanovia 654A-36) equipped with a Pyrex filter which limits the radiation to wave lengths greater than 300 nm(Fig. XIV) was employed as a light source. The total energy emitted is about 10 times that for the medium pressure arcs; the emission is almost continuous in nature and is richer in longer wave length light than the medium- and low-pressure arcs.[31] The use of the medium-pressure arc lamps for the Barton reaction is, therefore, inapplicable and in our hands the reaction was unsuccessful in a trial case.

Benzene was found to be the best solvent using the criterion of minimum solvent nitroso dimer products.[26a] However, heptane and acetonitrile were also quite satisfactory[26a] and generally the highest

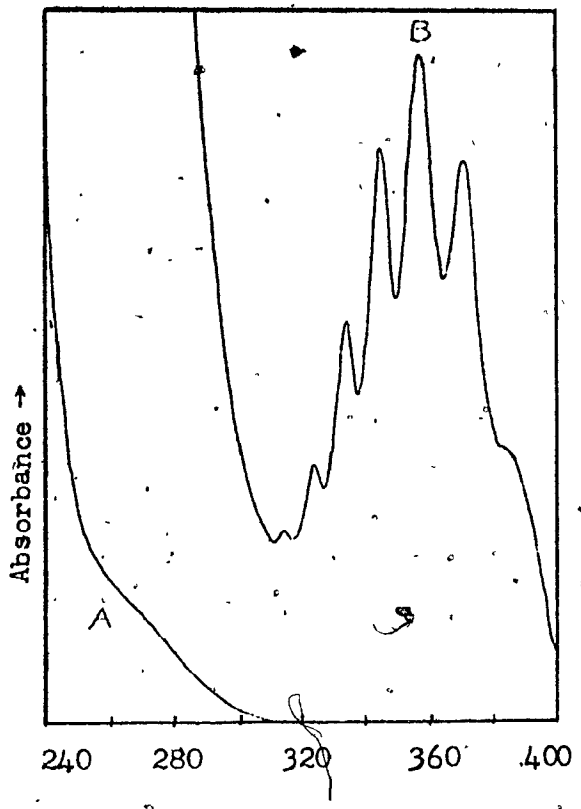


Fig. XIII. A, absorption spectrum of octyl nitrate in methanol; B, absorption spectrum of octyl nitrite in methanol.

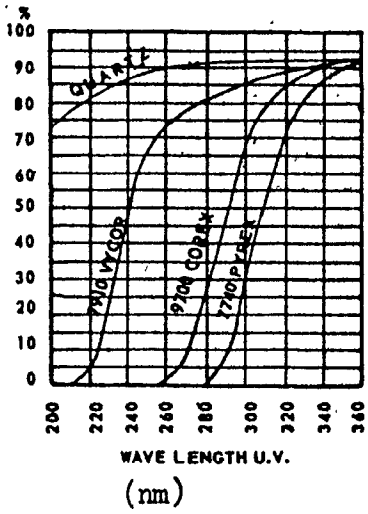


Fig. XIV

yields of nitroso dimer were obtained in solvents having poor radical chain transfer characteristics.[22] The effect of temperature on the yield of oxime has been reported; drastic reduction occurs at -55° while at + 60°, yields are only slightly better than room temperature.[22] No major trend in the temperature range 25-80° was reported by Barton.[33] In our hands, however, very poor yields of oxime resulted when the temperature was raised to near the boiling point of benzene. This reduction of oxime formation can be ascribed to the well known thermal sensitivity of nitrites and their tendency to undergo decomposition in the melt or in solution, especially in the presence of traces of impurities.[33]

In agreement with previous observations, no profound effect of

nitrite concentration on the yield of photolysis products was observed. However, it was noted that at high concentrations of starting material the reaction was incomplete and some starting material persisted even when the reaction time was increased to eight hours.

The photolysis was conducted while passing a stream of nitrogen through the solution. Oxygen interferes by combining with nitric oxide to form nitrogen dioxide which in turn combines with an alkoxy radical to form nitrates. The product of the Barton reaction is a nitroso-dimer ($R-\overset{+}{N}(O^-)=\overset{+}{N}(O^-)-R$) which isomerizes thermally to the oxime. The degree of formation of nitroso-dimer or oxime in the photochemical reaction was suggested to be delicately balanced by the equilibrium position between monomer and dimer. Factors affecting the constitution of the equilibrium mixture include the relative solubility of the dimer and the presence of trace impurities of hydroxylic materials which catalyze the isomerization of the nitroso monomer to oxime.[32] As observed above, heating the dimer in alcoholic media converts it to a monomer which in turn isomerizes to an oxime. The formation of nitroso dimers of steroids has been reported to be somewhat retarded, presumably because of steric factors.[106] Photolysis of the nitrite esters investigated in this work generally gave mixtures of dimer and oxime. By simply boiling the mixture in isopropanol for 15 to 30 minutes on the steam bath complete conversion to the oxime took place.

The yields of photolysis products(oximes) range to 45 % except in the case of 18-oximino-20α-hydroxypregn-4-en-3-one(38) which was obtained in 60 % yield(Table VII). The latter compound has been obtained in 63 % yield by Barton,[15d] the best yield yet reported for a nitrite ester photolysis. Generally, the yields of photolysis products of 20β-nitrite

Table VII. Yields of Oximes.

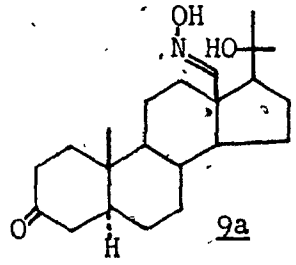
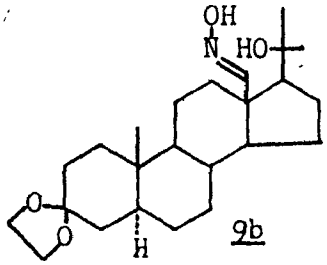
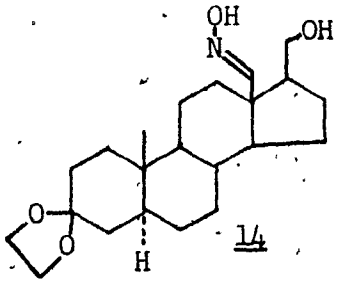
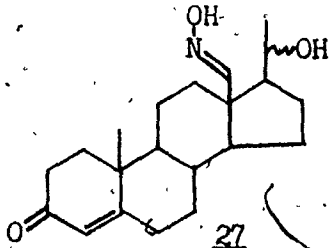
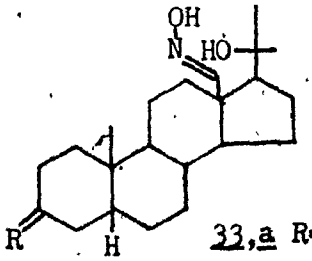
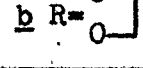
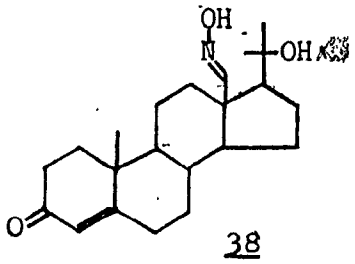
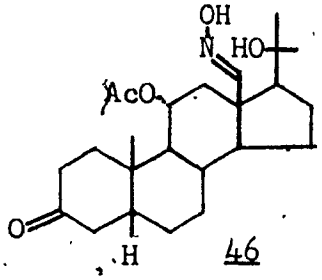
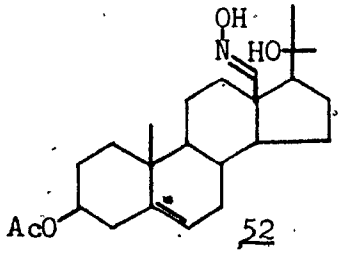
18-Oximino steroid	Photolysis time(h) (Starting material)	Yield (%)	Calculated / Found (Elemental analysis)	
 9a	1.7(8)	40.0	C, 72.59 H, 9.57 N, 4.03	72.48 9.65 3.97
 9b	1.7(10)	25	C, 70.55 H, 9.52 N, 3.58	*
 14	2.0(13)	~25	C, 69.99 H, 9.34 N, 3.71	 *
 27	1.2(26) 1.8(26) 4.0(26)	23.1 31.7 13.7	C, 73.01 H, 9.04 N, 4.05	72.85 8.88 3.97
 33,a R=O b R= 	2.0(32)	33a 6.2 33b 24.7 30.9	33b C, 70.55 H, 9.53 N, 3.58	 70.58 9.54 3.49

Table VII. continued

 38	2.0(37)	60** (63)[15d]	C, 73.01 H, 9.04 N, 4.05	*
 46	2.0(45) 2.5(48)	43.5 45.0	C, 70.92 H, 9.06 N, 3.60	*
 52	1.6(51) 4.3(51) 7.0(51)	24** 26.2 24.7 (23.3)[10b]	C, 70.92 H, 9.06 N, 3.60	71.16 9.09 3.50

* These compounds were not analyzed.

** These compounds have been previously prepared by Barton, et al. Yields obtained by these workers are shown in parentheses.

esters is much lower than for the 20α-isomers due to steric factors. It has been observed that in order to bring the alkoxy group of the 20β-isomer into the vicinity of 18-methyl group, greater Van der Waals repulsion between 21-methyl and C_{12}-methylene groups are encountered than in the case of 20α-isomer where there is virtually no such large non-bonded interaction.[72a] Because of these conformational factors, the reported highest yield of photolysis product from a 20β-nitrite ester is ~35 %.

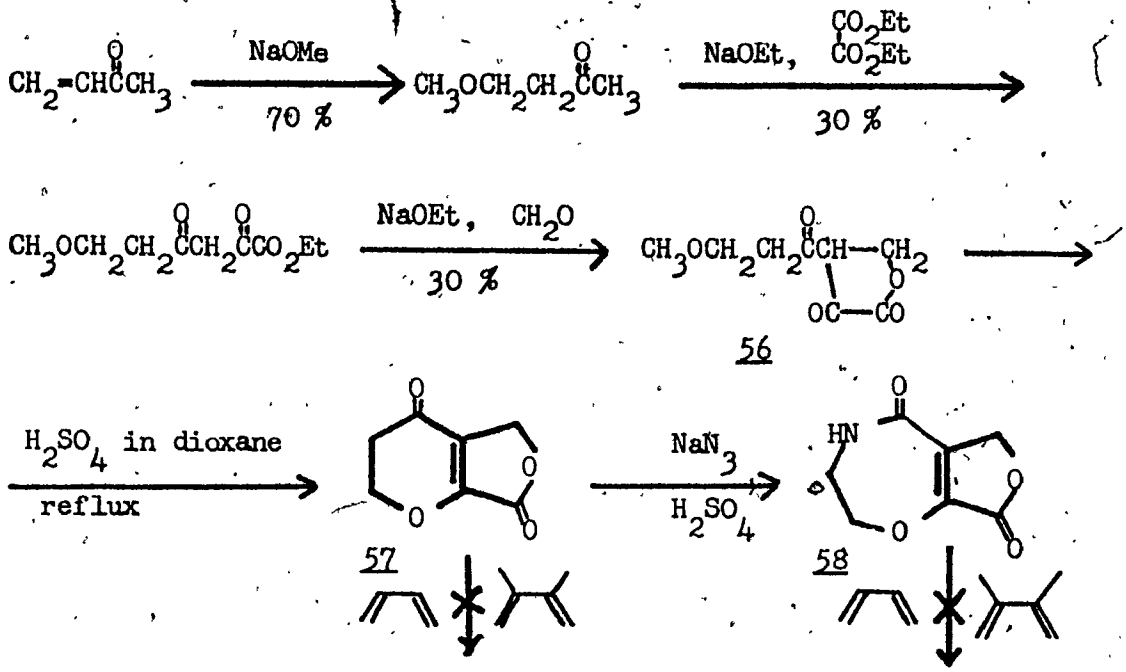
The higher yields(45 and 43.5 %)(Table VII) which were obtained by photolysis of the 20β-nitrite esters(48 and 45) can also be explained by steric factors. The repulsion between hydrogen atoms at C_1 and the 11α-acetoxy group will change the conformation of ring C and consequently the dihedral angle of rings C and D. This change increases the distance between C_{12} and C_{21} making attack at C_{18} easier. A better yield of C_{18} functionalized steroids in this type of system has also been reported in the hypoiodite reaction.[13b]

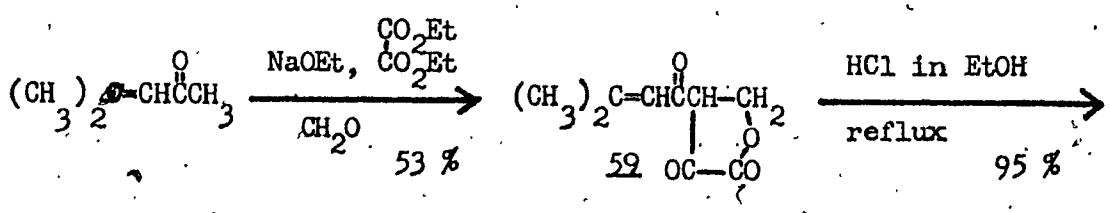
Under the conditions of photolysis, the ketal groups are either partially removed in the case of the compound 32 or completely removed from 3-dimethyl ketal 45. We have noted that the yield of photolized product is improved and separation becomes easier when non-ketalized compounds are photolized.

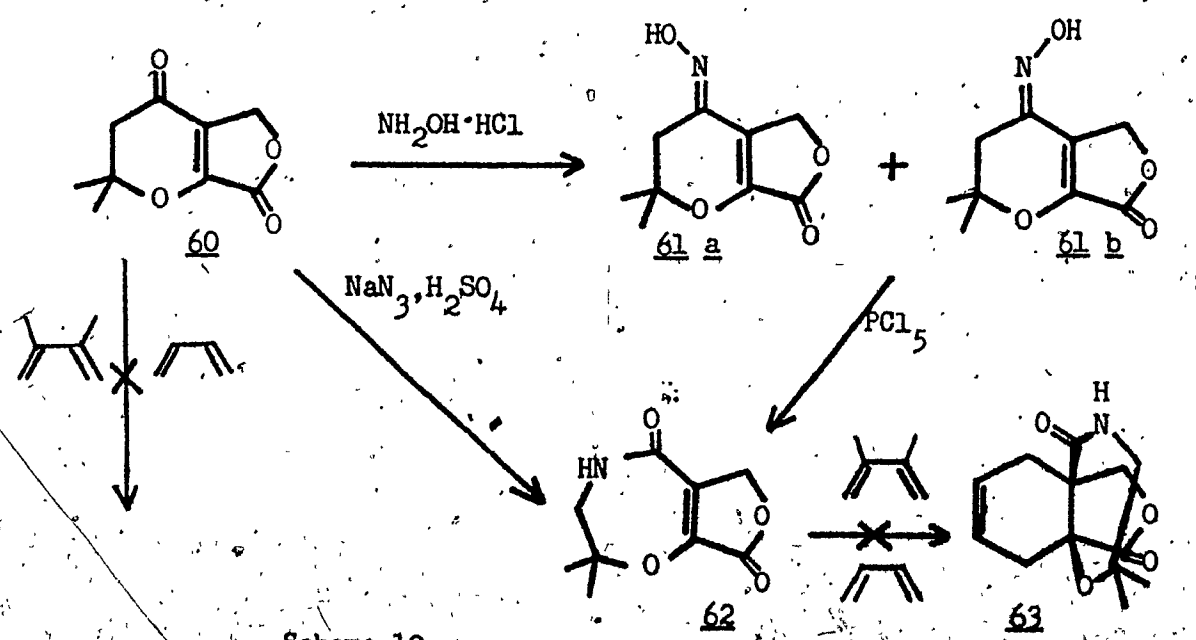
Preparation of the Model Lactams(58 and 62).

An attempt has also been made to prepare C/D ring systems similar to that encountered in Batrachotoxin. For this purpose the synthetic sequences, 56 →→ 58 and 59 →→→ 62, were carried out(Scheme 12).

For the synthesis of the dihydro-γ-pyrones(57 and 60), a series of Claisen condensations and cyclizations were utilized. Condensation of diethyl ester of oxalic acid with the appropriate methyl ketone gave a 2,4-diketo ester which in its sodium enolate form was treated with formaldehyde to yield α-keto-β-acyl-butyrolactones(56 and 59). These lactones were cyclized under dehydrating conditions to the dihydro-γ-pyrones. The preparation of the lactams(58 and 62) from the γ-pyrones was effected with hydrazoic acid generated in situ by the action of concentrated H_2SO_4 on sodium azide.


NaOMe
70 %
NaOEt, CO2Et CO2Et
30 %
NaOEt, CH2O
30 %
56
H2SO4 in dioxane
reflux
NaN3
H2SO4
57
58


NaOEt, CO2Et CO2Et
CH2O
53 %
59
HCl in EtOH
reflux
95 %

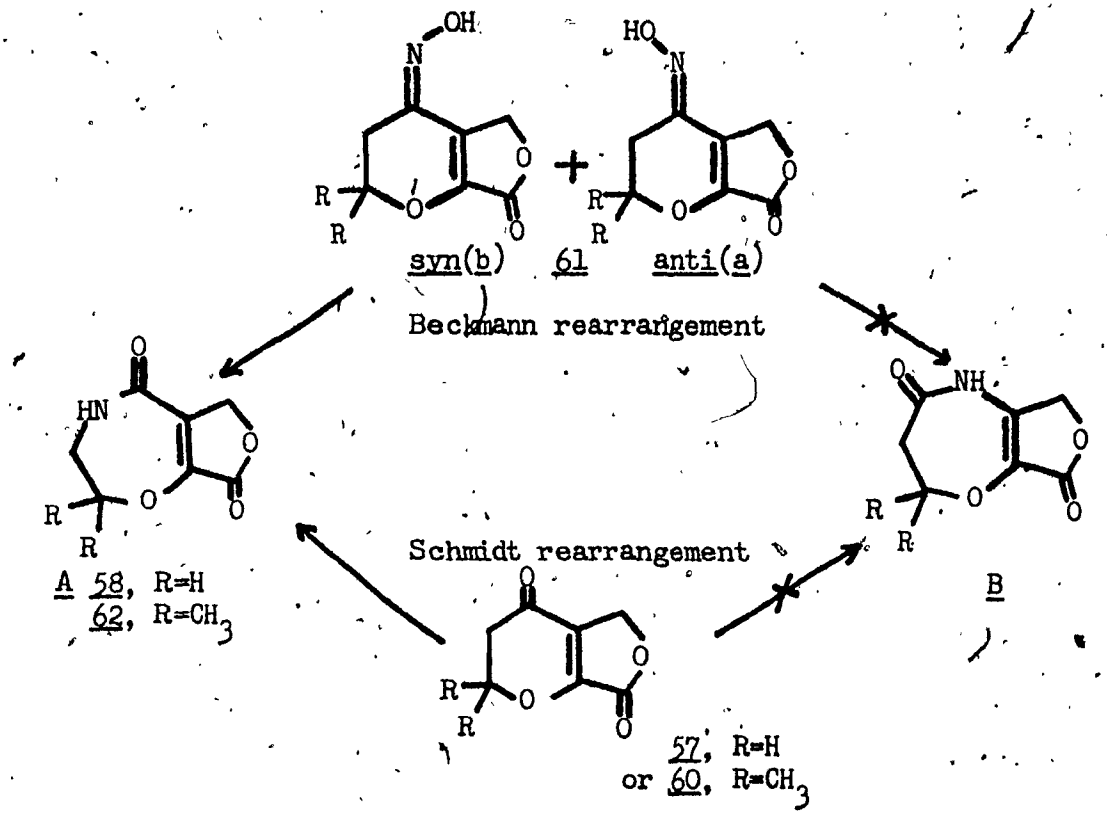

NH2OH·HCl
60
61 a
61 b
NaN3, H2SO4
PCl5
62
63

Scheme 12

The structures of the Schmidt rearrangement products 58 and 62 were confirmed by NMR. The methylene group adjacent to -NH appeared as a multiplet in the case of 58(at δ3.68) and as a doublet for 62(at δ3.44). The methylene group adjacent to carbonyl in the starting material gave a triplet at δ2.78 for 57 and a singlet at δ2.70 for 60. The lactam 62 was also prepared by a Beckmann rearrangement of the oxime 61 using phosphorus pentachloride in tetrahydrofuran; as indicated by NMR, the oxime was present in both syn- and anti-forms to an equal extent. However, it was assumed that the Beckmann rearrangement took place with only the syn-isomer(OH and C=C syn), since phosphorus pentachloride in non-polar solvents is known to be the reagent least prone to catalyze prior isomerization.[110] An attempt to recover and identify the unreacted anti-oxime or other by-product failed.

The Beckmann rearrangement of the mixture of syn- and anti-oximes may in principle give two products, since the substituent located anti to the leaving group(in this case $-OPCl_4$) migrates efficiently, regardless whether the substituent is alkyl or olefinic.[109] In our hands, however, only lactam A(Scheme 13) was obtained from the Beckmann and Schmidt rearrangements. The failure to produce lactam B(Scheme 13) can be explained in terms of steric effects in the bridged ion transition state.

As observed by Sato,[109] if a bridged ion transition state occurs in the migration of an olefinic group, the developing orbital on migrating carbon atom(C_3) should be in a position of maximum overlap with the developing vacant p-orbital(shaded) of C_4 and N for the stabilization to be most effective(Fig. XV). The latter must be at right angles to the existing p-orbital of carbon-nitrogen double bond, causing



Scheme 13

the bonds C_5-C_4-N to be colinear. Then, for the maximum orbital overlap, the plane(σ_1) including C_5, C_4, N, and the developing p-orbital(shaded)

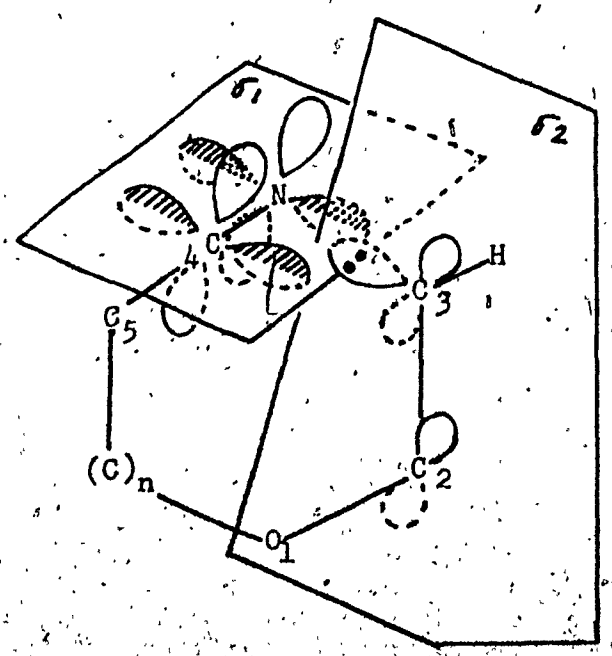


Fig. XV

should be perpendicular to the plane(σ_2) of the O_1-C_2-C_3 system. It is assumed that the orbital of C_3 would partially overlap with the developing vacant p-orbital of C_4 and N and partially with the p-orbital of C_2(with twisting). On this basis it has been found that only a few derivatives of the cyclohexene ketoxime system undergo a Beckmann rearrangement with migration of the olefinic group.[111] More generally speaking, however, cyclohexene ketoximes do not undergo Beckmann rearrangement with migration of the olefinic moiety. This observation has been attributed to the distortion of bond angles which the molecule must undergo in order to assume the conformation required for maximum orbital stabilization.

EXPERIMENTAL

General.

1) Melting points were determined with a Gallenkamp MF-370 melting point apparatus and were uncorrected.

2) Infrared spectra were obtained employing a Perkin-Elmer 457 spectrometer. A Bausch and Lomb UV-505 spectrometer was used to record ultraviolet spectra(ethanol was used as solvent in all cases).

3) Optical rotatory dispersions were measured in a 0.1-dm cell with Jasco Model ORD/UV-5. Optical rotations were also obtained with this instrument in $CHCl_3$ (c = 1) at 23°.

4) NMR spectra were obtained using $CDCl_3$ as solvent unless stated otherwise with a Varian A-60A instrument using tetramethylsilane as internal standard.

5) Mass spectra were run employing an Hitachi, Type RMU-7, double focusing mass spectrometer operating at 70 e.v. Generally samples were volatilized in the indicated temperature range, 150-300°.

6) Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921.

7) All reactions were performed initially on 3-15 mg quantities and were monitored by TLC, IR, and UV. Subsequently the reactions were scaled up to 50-300 mg for the purpose of obtaining NMR data and establishing optimum reaction conditions and finally to the gram scale.

8) TLC plates for monitoring reactions were prepared in 250 μm thicknesses with Silica Gel 7GF, Baker TLC Reagent. The spots were detected by UV lamp and by development with a 50 % H_2SO_4 spray. For

purposes of preparative TLC, plates coated to a thickness of 1 mm were used. For column chromatography, Alumina(Brockman Activity I, 80-200 mesh, Fisher Scientific Co.), Silica Gel(Davison Commercial Grade H-Type, 100-200 mesh, Grace Chemical Co.), and Florisil(F-100, 60-200 mesh, Fisher Scientific Co.) were used.

9) Photolysis of nitrite esters.[15]

The apparatus consisted of a borosilicate vessel with a gas inlet tube at the bottom and a cooling jacket, a water-cooled borosilicate immersion well, and a 200 watt Hanovia high pressure mercury arc lamp equipped with a Pyrex filter sleeve.

The steroid nitrite ester in dry benzene was irradiated at 10-15°, while a stream of nitrogen was bubbled through the reaction mixture during the course of the photolysis. The reaction was monitored by TLC and the reaction mixture was concentrated and chromatographed. In cases when the nitroso dimer constituted a large proportion of the product, the residue was heated with isopropyl alcohol prior to chromatography.

10)Preparation of nitrite esters.

A solution of the 20-hydroxy steroid in dry pyridine was cooled in a dry ice-CCl_4 bath(-10 to -15°) and stirred continuously while nitrosyl chloride was allowed to bubble through the solution until a persistent deep blue color was observed. After cooling and stirring a further 30 minutes the reaction mixture was quenched by slowly pouring it into cold water with stirring. The solid initially precipitated was occasionally sticky, but hardened after stirring for about 30 minutes. The precipitate was filtered, washed with water,

dried well in vacuo, and used for next reaction without further purification.

17β-Hydroxyandrost-5-en-3-one cyclic 3-(ethylene acetal)(2).

A stirred mixture of 9.0 g(31 mmoles) of testosterone(1) in 27 ml of freshly distilled ethylene glycol and 810 ml of benzene was slowly distilled until approximately 50 ml of distillate was obtained. The residual reaction mixture was treated with p-toluenesulfonic acid(0.9 g, 0.1 part by weight) and refluxed for at least 3.5 hours with continuous removal of water by means of a Dean-Stark phase separator. When the bulk of the water had been removed, P_2O_5 was added to the arm of the trap and refluxing of the reaction solution was continued overnight.

Saturated sodium bicarbonate solution was added to the cooled reaction mixture and the benzene layer separated. After washing the benzene layer with water and drying over anhydrous sodium sulfate, the solution was concentrated to low volume under reduced pressure. Methanol and a few drops of pyridine were added and the solution was reconcentrated. The latter process was repeated until most of the benzene had been replaced by methanol. The cooled concentrated methanol solution yielded 8.7 g(83.9 %) of 2, which when recrystallized from acetone gave crystals, mp 184.5-186°(lit.[4] mp 184-185°); IR($CHCl_3$) 3610 and 3455(OH) and 1090(C-O) cm^{-1}; NMR δ0.76(18-CH_3), 1.04(19-CH_3), 3.52(broad, 17-CH), 3.93(OCH_2CH_2O), and 5.37(broad, 6-CH).

17β-Hydroxy-5α-androstan-3-one cyclic 3-(ethylene acetal)(3).

A solution of the Δ^5-3-ketal(2; 4.0 g, 12 mmoles) in methanol(520 ml; solvent grade) was hydrogenated at room temperature and atmospheric pressure employing 10 % Pd/C(1.3 g) as catalyst. The catalyst was

removed by filtration when uptake of hydrogen had ceased and the solution, to which a few drops of pyridine had been added, was concentrated until precipitation of product occurred. The filtered hydrogenated product was washed with methanol to yield 3(2.8 g, 69.6 %), mp 168-170°(lit.[112] mp 171-173°; lit.[4] 163-165°); IR($CHCl_3$) 3600 and 3420(OH) and 1075(C-O) cm^{-1}.

5α-Androstane-3,17-dione cyclic 3-(ethylene acetal)(4).

A solution of 2.81 g(8.4 mmoles) of 3 in 20 ml of pyridine was treated in a nitrogen atmosphere with chromium trioxide(4.2 g) dissolved* in 30 ml of pyridine.[6,7] The reaction mixture was stirred overnight at room temperature and subsequently poured into 160 ml of water and the product was extracted with ether. The ethereal solution was washed succesively with dil. HCl solution, 10 % $NaHCO_3$ solution, and water, and dried over anhydrous sodium sulfate.

Concentration of the solution with a few drops of pyridine yielded 2.61 g(93.1 %) of 4, sufficiently pure for the next reaction. Recrystallization of the product from ligroin(bp 63-75°) gave crystals, mp 155-156.5°(lit.[55a] mp 157°); IR($CHCl_3$) 1730(C=O) and 1095(C-O) cm^{-1}; NMR δ 0.86(overlapped 18- and 19-CH_3) and 3.95(OCH_2CH_2O); m/e 332(M^+).

5α-Pregn-cis-$\Delta^{17(20)}$-en-3-one cyclic 3-(ethylene acetal)(5): Wittig[46,47] reaction of 4.

Potassium t-butoxide(5.47 g, 44 mmoles) was added in three portions to a cooled stirred solution of 4(3.0 g, 9 mmoles) and ethyltriphenyl-

* The preparation of the CrO_3-pyridine complex is potentially extremely hazardous if the precise conditions given in references[45,60] are not followed.

phosphonium iodide[46] (20.25 g, 44 mmoles) in DMSO (75 ml). The reaction solution was maintained in a nitrogen atmosphere and was observed to turn a deep red colour immediately. The reaction mixture was stirred overnight and then poured into ice-water. The solid suspension in water was extracted with ligroin (35-60°; 500 ml x 3) and the ligroin extractions were washed with water, dried (anhydrous Na_2SO_4) and concentrated in vacuo to small volume in the presence of a few drops of pyridine. Repeated addition of methanol and reconcentration to small volume gave the Δ^{17}-olefin 5 which was filtered and washed with a little methanol to yield 2.86 g (92.0 %) of product. Recrystallization from methanol gave 5, mp 121.5-123°; IR ($CHCl_3$) 1090 (C-O) cm^{-1}; NMR δ 0.83 (18-CH_3), 0.87 (19-CH_3), 3.90 (OCH_2CH_2O), and 5.01 (broad, 20-CH). M/e 344.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.11; H, 10.53.

20β-Hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal) (6): Hydroboration[46,47] of 5.

1 M BH_3-THF complex (25 ml) was added drop by drop to a stirred solution of 5 (2.25 g, 6.5 mmoles) in 90 ml of dry THF. The reaction was carried out in an atmosphere of nitrogen and maintained at room temperature. After stirring for 70 minutes, 45 ml of 10 % NaOH solution was cautiously added dropwise, while maintaining the temperature below 17°. After cooling to 0° in an ice-salt bath, 25 ml of 30 % H_2O_2 was added dropwise to the stirred reaction mixture over a 10-20 minute period. The reaction mixture was then partitioned between ethyl acetate and cold water and the organic layer was washed with 10 % $NaHSO_3$ solution and water. The ethyl acetate solution was dried (Na_2SO_4) and concentrated. Repeated addition of ligroin (63-75°) and reconcentration gave 6 (1.76 g, 74.4 %),

mp 165.5-166°; IR($CHCl_3$) 3600 and 3450(OH) and 1090(C-O) cm^{-1}; NMR δ0.75 (18-CH_3), 0.82(19-CH_3), 1.13(doublet, J=6 Hz, 21-CH_3), 3.51(broad, 20-CH) and 3.90(OCH_2CH_2O).

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.20; H, 10.57. Found: C, 76.07; H, 10.42.

20β-Hydroxy-5α-pregnan-3-one(7).

The 20β-hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(6; 0.35 g, 0.97 mmoles) was refluxed for an hour in acetone(35 ml) in the presence of water(3 ml) and p-toluenesulfonic acid(45 mg). The solution, after dilution with water, precipitated a solid which was filtered and dried to give 0.274 g(89.0 %) of the deketalized product. Three recrystallizations from acetone gave pure 7, mp 191.5-.94°(lit.[41] mp 194-196°); IR($CHCl_3$) 3440(OH) and 1700(C=O) cm^{-1}; NMR δ0.78(18-CH_3), 1.02(19-CH_3), 1.14(doublet, J=6 Hz, 21-CH_3), and 3.73(broad, 20-CH).

20β-Hydroxy-5α-pregnan-3-one 20-nitrite ester(8).

The 20-hydroxy steroid(7; 4.87 g, 15.3 mmoles) was dissolved in 100 ml pyridine and treated with nitrosyl chloride according to the general procedure given on p 58, to give 4.5 g(84.3 %) of 8.

18-Oximino-20β-hydroxy-5α-pregnan-3-one(9a).

The nitrite ester(8; 1.0 g, 2.9 mmoles) was dissolved in 35 ml of dry benzene and photolized for 1.7 hours according to the general procedure(p 58). The product oxime was eluted from neutral alumina(50 g) in the ether fraction to give 0.4 g(40 %) of 9a. Two recrystallizations from ethyl acetate gave crystals of 9a, mp 181.5-183.5°; IR($CHCl_3$) 3670 and 3190(OH) and 1695(C=O) cm^{-1}; NMR δ0.99(19-CH_3), 1.19(doublet,

J=6.5 Hz, 21-CH_3), 3.93(broad, 20-CH), 7.50(CH=N), and 9.73(broad, C=N-OH).

Anal. Calcd for $C_{21}H_{33}N_1O_3$: C, 72.59; H, 9.57; N, 4.03. Found: C, 72.48; H, 9.65; N, 3.97.

18-Oximino-20β-hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(9b).

The nitrite ester(10; 0.16 g, 0.41 mmoles) in 40 ml benzene was photolyzed according to the general procedure. The photolyzed residue was dissolved in a small amount of methanol and methylene chloride and chromatographed on alumina(40 g). The product was eluted with ligroin (63-75°) : benzene(1 : 1) and was recrystallized from benzene-hexane to give 9b(40 mg, 25 %). IR($CHCl_3$) 3480(OH), 1625(C=N), and 1095(C-O) cm^{-1}; NMR($CDCl_3$ + 2 drops of DMSO-d_6) δ0.76(19-CH_3), 1.11(doublet, J=6 Hz, 21-CH_3), 3.43(broad, 20-CH), 3.92(OCH_2CH_2O), 7.39(CH=N), and 9.67 (broad, C=N-OH).

20β-Hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal), 20-nitrite ester(10).

A solution of 6(0.2 g, 0.55 mmoles) in dry pyridine(12 ml) was treated according to the general procedure to give 0.19 g(89 %) of the nitrite ester 10. NMR δ0.63(18-CH_3), 0.78(19-CH_3), 1.31(doublet, J=6 Hz, 21-CH_3), 3.83(OCH_2CH_2O), and 5.33(broad, 20-CH).

21-Nor-cis-$\Delta^{17(20)}$-5α-pregnan-3-one cyclic 3-(ethylene acetal)(11): Wittig reaction of 4.

Sodium hydride(50 % dispersion in mineral oil; 0.72 g, 15 mmoles) was washed three times with n-hexane and dried under a nitrogen stream. Dry DMSO(10.8 ml) was added to this and the mixture was stirred and heated to 70-75° under nitrogen for 30-40 minutes. The resulting light

green solution of the sodium methylsulfinate was cooled to room temperature and a warm solution of methyltriphenylphosphonium bromide (5.36 g, 15 mmoles) in DMSO was rapidly added, producing a deep red colouration in the solution. A solution of 5α-androstane-3,17-dione cyclic 3-(ethylene acetal)(4; 1.02 g, 3 mmoles) in 10 ml DMSO was then added rapidly to the above methylidenetriphenylphosphorane solution. The mixture was stirred under nitrogen at room temperature for 39 hours and poured into ice-water. Subsequent petroleum ether extraction, washing with water, drying, and evaporation yielded a solid residue. The residue was redissolved in ether and a few drops of pyridine and reconcentrated with several additions of methanol until maximum precipitation was attained. The precipitate in methanol was cooled and filtered to give 11(0.98 g, 96.8 %), mp 128-130.5°; NMR δ0.76(18-CH_3), 0.83(19-CH_3), 3.92(OCH_2CH_2O), and 4.61(multiplet, 20=CH_2).

17β-Hydroxymethyl-5α-androstan-3-one cyclic 3-(ethylene acetal)(12): Hydroboration of 11.

A solution of 11(0.14 g, 0.41 mmoles) in 7 ml THF was treated(as described for the preparation of 6 on p 61) with 1.4 ml of 1 M BH_3-THF, 1.5 ml of 10 % NaOH solution, and 1.4 ml of 30 % H_2O_2. The product 12 (0.105 g, 71.1 %), after recrystallization from hexane gave crystals, mp 167.5-169°; IR($CHCl_3$) 3620 and 2470(OH) and 1095(C-O) cm^{-1}; NMR δ0.65 (18-CH_3), 0.83(19-CH_3), 3.63(broad, 20-CH_2), and 3.92(OCH_2CH_2O). M/e 348.

17β-Hydroxymethyl-5α-androstan-3-one cyclic 3-(ethylene acetal), 20-nitrite ester(13).

The nitrite ester was prepared in 86.9 % yield from the alcohol 12 by the general procedure. IR($CHCl_3$) 1640(ONO) and 1095(C-O) cm^{-1}; NMR

δ 0.70(18-CH_3), 0.83(19-CH_3), 3.92(OCH_2CH_2O), and 4.67(broad, 20-CH_2).

18-Oximino-17β-hydroxymethyl-5α-androstan-3-one cyclic 3-(ethylene acetal) (14).

Photolysis of the nitrite ester(13; 70 mg) in 10 ml benzene yielded a mixture of products, one of which showed a spot (estimated as approximately 25 % of the total product) on TLC lower than the alcohol 12 and the starting material 13. An attempt to isolate and identify this product failed.

5α-Pregnane-3,20-dione(15).

The 20β-hydroxy-5α-pregnan-3-one(7; 0.1 g, 0.32 mmoles) was treated with a CrO_3-dil. acetic acid mixture. After stirring over-night the reaction mixture was poured into water and filtered. The well washed solid was dissolved in acetone and concentrated with addition of ligroin (63-75°), to give 15(80 mg, 80 %); IR($CHCl_3$) 1700(C=O) cm^{-1}; NMR δ0.65 (18-CH_3), 1.02(19-CH_3), and 2.11(doublet, J=6.5 Hz, 21-CH_3).

This compound was required for the purposes of comparison(NMR) only and was not further utilized.

20β-Hydroxy-5α-pregnan-3-one 20-acetate(16).

The mixture of 20β-hydroxy-5α-pregnan-3-one(7; 50 mg, 0.16 mmoles), acetic anhydride and pyridine was stirred overnight and then treated with water. The precipitate was filtered and washed well with water to yield 57 mg(100 %) of 16. NMR δ0.64(18-CH_3), 0.99(19-CH_3), 1.12(doublet, J=6 Hz, 21-CH_3), 1.96($OCCH_3$), and 4.75(broad, 20-CH).

3,3-Dimethoxy-20β-hydroxy-5α-pregnane 20-acetate(17).

The 3-keto-20β-acetoxy compound(16; 50 mg, 0.14 mmoles) in absolute

methanol(4 ml) was refluxed for 3 hours in the presence of p-toluenesulfonic acid and then cooled in the refrigerator. The crystals formed were filtered and washed with methanol to give 53 mg(94 %) of 17, mp 127.5-130.5°; IR(KBr) 1727(C=O of acetate), 1230(C-O of ester), and 1097 and 1045(C-O of ketal) cm^{-1}; NMR δ0.60(18-CH_3), 0.77(19-CH_3), 1.12(doublet, J=6 Hz, 21-CH_3), 1.96(O$\overset{O}{\overset{\|}{C}}CH_3$), 3.07 and 3.12(6H of ketal), and 3.38(broad, 20-CH).

20α-Hydroxypregn-5-en-3-one cyclic 3-(ethylene acetal)(18a) and its 20β-isomer(18b).

The above epimeric compounds were prepared separately by the same method. A mixture of the 20α- or 20β-hydroxy-3-keto steroid(0.5 g, 1.58 mmoles), ethylene glycol(3.0 ml) and p-toluenesulfonic acid(0.1 g) were refluxed in benzene for 22 hours with continuous removal of water by means of Dean-Stark phase separator. The workup followed the procedure previously described on p 59 for the preparation of 2 to give 18a or 18b(0.418 g, 73 %). NMR of 18a δ0.68(18-CH_3), 1.02(19-CH_3), 1.20(doublet, J=6 Hz, 21-CH_3), 3.60(broad, 20-CH), 3.85(OCH_2CH_2O), and 5.22(broad, 6-CH); 18b δ0.77(18-CH_3), 1.03(19-CH_3), 1.12(doublet, J=6 Hz, 21-CH_3), 3.63(broad, 20-CH), 3.85(OCH_2CH_2O), and 5.20(broad, 6-CH).

20α-Hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(19a) and its 20β-isomer(6).

The Δ^5-unsaturated steroids(18a or 18b; 0.3 g, 0.83 mmoles) were hydrogenated in ethanol(200 ml) with 0.25 g of 5 % Pd/C catalyst according to the procedure on p 59 for preparation of 3, yielding 0.25 g(83 %) of the reduction products. NMR of 19a δ0.66(18-CH_3), 0.81 (19-CH_3), 1.20(doublet, J=6 Hz, 21-CH_3), 3.55(broad, 20-CH), and 3.85

(OCH_2CH_2O); 6 prepared from 18b was found to be identical to the one prepared from the Δ^{17}-olefin compound 5(p 61).

20α-Hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal) 20-tosylate (20a) and its 20β-isomer(20b).

The 20α- or 20β-hydroxy steroid(0.2 g, 0.55 mmoles) and p-toluenesulfonyl chloride(0.4 g) in pyridine were stirred for 20 hours at room temperature and then poured into ice-water. The precipitate was filtered and dried well to give 0.25 g(88 %) of the 20-tosylate which was then used for the next reaction without further purification.

A mixture of 5α-pregn-trans-$\Delta^{17(20)}$-en-3-one cyclic 3-(ethylene acetal) (21a) and its cis-$\Delta^{17(20)}$-ene isomer(5).

Refluxing a collidine solution of 20α-tosylate(20a) for 2 hours gave a mixture which was mostly composed of 21a and 5(~15 % of 21a). The mixture of 21a and 5 could be separated from by products by preparative scale TLC. NMR δ 0.73(18-CH_3), 0.83(19-CH_3), 3.88(OCH_2CH_2O), 5.12(broad, 20-CH), and 0.87(low intensity, 19-CH_3 of cis-isomer).

The same treatment of the 20β-tosylate as above gave 21a and 5 in equal amounts. TLC showed more by-products than in the case of the 20α-tosylate. Both 21a and 5 were separated together from the mixture by preparative scale TLC. NMR 0.73 : 0.83 : 0.87 = 1 : 2 : 1.

Progesterone 3-pyrrolidinylenamine(23), 20β-hydroxyprogesterone 3-pyrrolidinylenamine(24, a and b), and 20β-hydroxypregn-4-en-3-one (25, a and b)(23 → 24a,b → 25a,b).

These compounds were prepared according to the method of A. H. Nathan and P. E. Marlatt.[88] The yield 73.2 % for 25 is based on

progesterone(22). UV of 23: 280(20,500). M_D of 23: -128°.

Preparation of 20α-hydroxypregn-4-en-3-one(25a) and of its 20β-isomer (25b).

Method a). Separation of the mixture(25, a and b), prepared by the method of Nathan and Marlatt,[88] employing a dry-column technique.[89]

Preparation of column: Aluminum oxide(Baker Analyzed Reagent, 0537) was deactivated to grade II-III by addition of water(aluminum oxide : water = 100 : 4-5 by weight) and equilibrated by rotating for 3-5 hours. The base of the column was packed with glass wool and the column was charged, with stop-cock open, by pouring in the deactivated adsorbent slowly through a fine tube attatched to a funnel. Even packing was ensured by means of a vibrator. The sample to be chromatographed was dissolved in a small quantity of methylene chloride and mixed with five times its weight of deactivated adsorbent. The excess solvent was evaporated(at 30-40°) to dryness with a rotatory evaporator. The sample-adsorbent mixture was then distributed evenly on the top of the column and covered with a small layer of sand and a filter paper.

The eluting solvent, chloroform, chosen on the basis of TLC results,

Table VIII. Separation of 20β- and 20α-hydroxypregn-4-en-3-one from the mixture(25, a and b).

Loaded	Adsorbent wt. and column dimensions	20β-ol	20β- and 20α-ol	20-ol
1 g	110 g(4/5" x 15")	0.434 g	0.374 g	0.228 g
5 g	700(1 1/4" x 37")	2.37 g	1.40 g	1.13 g
11 g	1200(2" x 25")	5.565 g	2.25 g	2.48 g

was applied to the top under a constant liquid head of 3-5 cm, achieved by use of a stoppered separatory funnel. When the solvent front reached the bottom of the column, the rate of the flowing was controlled by means of a stop-cock and 15 ml frattions were collected(Table VIII).

Method b).

20α-Hydroxypregn-4-en-3-one(25a)(22 → 34 → 35 → 36 → 18a → 25a).

Pregn-5-ene-3,20-dione cyclic 3-(ethylene acetal)(36) was prepared from progesterone(22) via the 20-cyanohydrin(34) and the ketalized compound(35) by the method of A. Ercoli.[105] The 20-keto compound(36) was reduced with sodium in refluxing 2-propanol and deketalized according to the method of Lee and Wolff.[72c] Recrystallization from hexane-benzene gave pure 25a, mp 161-163°(lit.[72c] mp 162-163.5°); NMR δ 0.73(18-CH_3), 1.19(19-CH_3), 1.26(doublet, J=6 Hz, 21-CH_3), 3.73 (broad, 20-CH), and 5.78(4-CH).

20β-Hydroxypregn-4-en-3-one(25b).

The mixture of pregn-4-ene-3α,20β- and pregn-4-ene-3β,20β-diols(39) was prepared by sodium borohydride(2 g) reduction of progesterone(4 g) in 40 ml of methanol and 2 ml of H_2O. The reaction mixture was heated under reflux for 1.5 hours and after cooling the mixture was poured into dil. acetic acid solution. Upon further cooling in an ice-bath(1-2 hours), the solid reduction product precipitated and was isolated by filtration. The reduction product was stirred for one day in 300 ml of chloroform with 30 g of manganese dioxide in order to effect the selective oxidation of the allylic alcohol. The metal oxides were removed by filtration and washed thoroughly with hot chloroform. The combined chloroform extracts were evaporated to yield a solid which was

recrystallized from ether-ligroin(63-75°) to give 2.8 g(70 %) of 25b, mp 173-175°(lit.[72c] mp 172-173.5°); NMR[72c] δ0.81(18-CH_3), 1.14(doublet, J=6 Hz, 21-CH_3), 1.20(19-CH_3), 3.77(broad, 20-CH), and 5.77(4-CH).

20β-Hydroxypregn-4-en-3-one nitrite ester(26, a and b).

A mixture of 20α- and 20β-hydroxypregn-4-en-3-one(25, a and b) was treated with nitrosyl chloride at -5 to -15° according to the general procedure for the preparation of nitrite esters described on p 58. The yield was 94.5 % based upon the alcohol.

18-Oximino-20-hydroxypregn-4-en-3-one(27, a and b).

A solution of the nitrite ester(26a,b; 6.0 g; 17.3 mmoles) in dry benzene(550 ml) was irradiated(10-18°) for an hour 50 minutes. After evaporation of the benzene, the residue was dissolved in a small quantity of chloroform and chromatographed on Florisil. The progesterone and 20-hydroxyprogesterone were eluted with benzene and benzene-ether (9 : 1) while the 18-oxime was eluted with benzene-ether(7 : 3). Evaporation of the solvent left 1.9 g(31.7 %) of the oxime. Recrystallization from acetone yielded the mixture of 27a and 27b, mp 224-226°[15d]; IR($CHCl_3$) 3590 and 3270(OH), 1660(α,β-unsaturated C=O), and 1615(conjugated double bond) cm^{-1}; NMR δ1.16(19-CH_3), 1.24(doublet, J=6 Hz, 20-CH_3),3.45(broad, 20-CH), 5.77(4-CH), 6.27(4-CH), 7.27 and 7.48(18-CH), and 8.48 and 8.90(broad, C=NOH); m/e 345(M^+).

Anal. Calcd for $C_{21}H_{29}N_1O_3$: C, 73.01; H, 9.04; N, 4.05. Found: C, 72.85; H, 8.88; N, 3.97.

Photolysis of 6 g and 9.5 g of the nitrite ester under the same conditions for one hour 10 minutes and 4 hours, respectively, gave a reduced yield of oxime 23.1 and 13.7 %, respectively.

20β-Hydroxy-18-nitrilo-4-pregnen-3-one(28, a and b).

The mixture of 20α- and 20β-hydroxy-18-oximes(27a,b; 1.12 g, 3.3 mmoles) was dissolved in 20 ml of pyridine and 20 ml of acetic anhydride and heated on a steam bath for one hour. The solution was concentrated under vacuum. The semi-solid residue was dissolved in 200 ml of 5 % alcoholic potassium hydroxide and refluxed under nitrogen for 2 hours. Neutralization with glacial acetic acid and concentration to low volume yielded after addition of water the steroid 28(0.17 g, 16 %), IR($CHCl_3$) 3600 and 3450(OH), 2230(C≡N), 1660(α,β-unsaturated C=O), and 1615 (conjugated double bond) cm^{-1}.

20β-Hydroxypregn-4-en-18-oic acid 18,20-Lactone(29, a and b).

The oxime(27a,b; 0.2 g, 0.58 mmoles) was dissolved in a mixture of 4 ml of 15 % aqueous $Na_2Cr_2O_7$ solution and 15 ml of glacial acetic acid. The oxidation was carried out for four hours and the reaction mixture was then poured into 350 ml of water. The resulting solid precipitate was filtered, washed with water and dried to give 0.15 g of 29(78.4 %). IR($CHCl_3$) 1745(lactone C=O), 1660(α,β-unsaturated C=O), and 1615(conjugated double bond); NMR δ1.28(19-CH_3), 1.39(doublet, J=6 Hz, 21-CH_3), 4.70(broad, 20-CH), and 5.74(4-CH).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.83; H, 8.65.

20β-Hydroxy-5β-pregnan-3-one(30).

The 20β-hydroxypregn-4-en-3-one(25b; 4.3 g, 13.6 mmoles) was dissolved in 0.1 N alcoholic-KOH solution(130 ml) and hydrogenated using 10 % Pd/C catalyst(0.6 g). After the uptake of hydrogen ceased, the catalyst was removed by filtration and the filtrate was diluted

with water to 1.5 l. The precipitate formed was filtered, washed with water and dried in vacuo to give 30(3.723 g, 86 %), mp 171-173°(lit.[41] mp 170-172); IR($CHCl_3$) 3590 and 3450(OH), and 1700(C=O) cm^{-1}; NMR δ0.78 (18-CH_3), 1.03(19-CH_3), 1.14(doublet, J=6 Hz, 21-CH_3), and 3.72(broad, 20-CH).

20β-Hydroxy-5β-pregnan-3-one cyclic 3-(ethylene acetal)(31).

A stirred mixture of 20β-hydroxy-5β-pregnan-3-one(30; 3.65 g, 11.5 mmoles) and 8.4 ml of freshly distilled ethylene glycol in 220 ml of dry benzene was slowly distilled in the presence of p-toluenesulfonic acid(0.35 g) until 40-50 ml of benzene had been removed. Subsequently the reaction mixture was refluxed for ten hours with continuous removal of water by means of a Dean-Stark trap. After workup in the manner described on p 59, the remaining residue was triturated with ligroin. An undissolved portion was removed by filtration and the filtrate was evaporated to yield 31(3.5 g, 83 %). Recrystallization from ligroin (100-115°) gave purified 31, mp 62-64.5°; IR($CHCl_3$) 3590 and 3450(OH) and 1090(ketal C-O) cm^{-1}; NMR δ 0.75(18-CH_3), 0.96(19-CH_3), 1.13 (doublet, J=6 Hz, 21-CH_3), 3.67(broad, 20-CH), and 3.94(OCH_2CH_2O).

20β-Hydroxy-5β-pregnan-3-one cyclic 3-(ethylene acetal) 20-nitrite ester(32).

The 20β-hydroxy compound(31; 2.81 g, 7.8 mmoles) was dissolved in 40 ml of pyridine and treated with nitrosyl chloride according to the general procedure, yielding 2.52 g(82.9 %) of 32. NMR δ0.67(18-CH_3), 0.98(19-CH_3), 1.18(doublet, J=6 Hz, 21-CH_3) and 5.37(broad, 20-CH).

18-Oximino-20β-hydroxy-5β-pregnan-3-one(33a) and its cyclic 3-(ethylene acetal)(33b).

The nitrite ester(32; 1.2 g, 3.1 mmoles) in 25 ml benzene was photolyzed for two hours according to the general method. The concentrated reaction solution was chromatographed on silica gel(60 g). The by-products, which showed a higher R_f than the oxime as determined by TLC were removed by elution with benzene and benzene : ether(9 : 1). Elution with benzene : ether(7 : 3) gave the 3-ethylene ketal oxime 33b (0.297 g, 24.7 %) which was followed by deketalized oxime 33a(0.066 g, 6.2 %). Three recrystallizations of 33b from ethyl acetate-ligroin(63-75°) gave purified oxime, mp 173.5-176°; IR($CHCl_3$) 3395(OH), 1620(C=N), and 1090(ketal C-O) cm^{-1}; NMR δ 0.88(19-CH_3), 1.12(doublet, J=6 Hz, 21-CH_3), 3.52(broad, 20-CH), 3.85(OCH_2CH_2O), and 7.22(N=CH). NMR for 33a δ 0.95(19-CH_3), 1.10(doublet, J=6 Hz, 21-CH_3), 7.37(N=CH), and 10.13 (C=N-OH).

Anal. Calcd for $C_{23}H_{37}N_1O_4$(33b): C, 70.55; H, 9.53; N, 3.58. Found: C, 70.58; H, 9.54; N, 3.49.

20α-Hydroxypregn-4-en-3-one 20-nitrite ester(37).

The 20α-hydroxy steroid 25a was treated with nitrosyl chloride according to the general procedure, yielding the nitrite ester 37 in 98 % yield.

18-Oximino-20α-hydroxypregn-4-en-3-one(38).

The nitrite ester 37(0.2 g, 0.58 mmoles) was dissolved in 20 ml of benzene and photolyzed for two hours. The residue after evaporation of the solvent was treated with isopropyl alcohol and chromatographed on silica gel(10 g). The fractions eluted with benzene : ether(the ratio

of solvents ranged from 7 : 3 to 5 : 5) were evaporated and the residue (0.12 g, 60 %) was recrystallized from ethylacetate-acetone to give 38, mp 183-185.5°(lit.[15d] mp 184-186).

11α-Hydroxypregn-4-ene-3,20-dione 11-acetate(41).

The 11α-hydroxyprogesterone(40; 12.5 g, 37 mmoles) in pyridine (70 ml) and acetic anhydride(70 ml) was stirred for 23 hours at room temperature and then diluted to 1.9 l with water. After cooling the solution in the refrigerator overnight, the precipitate formed was filtered, washed with water, and dried *in vacuo* to give 14 g(99.4 %) of 41, mp 173-174.5°. One recrystallization from isopropyl ether gave 41, mp 174-175.5°(lit.[107] mp 175-177°); NMR δ 0.76(18-CH_3), 1.28(19-CH_3), 2.05($OC(=O)CH_3$), 2.11(21-CH_3), 5.25(broad, 11-CH), and 5.79(4-CH).

11α-Hydroxy-5β-pregnane-3,20-dione 11-acetate(42).

The 11α-hydroxypregn-4-ene-3,20-dione 11-acetate(41; 3.0 g, 8.1 mmoles) was hydrogenated at atmospheric pressure employing 10 % Pd/C (0.3 g) as catalyst in ethanol(180 ml) containing 4.5 ml of triethylamine. The catalyst was removed by filtration and the filtrate was diluted to 1.1 l with water. Upon cooling the solution overnight in the refrigerator, the precipitate formed was filtered and then dried to give 42(2.63 g, 87.2 %), mp 143-146°(lit.[94] mp 148-149°); IR($CHCl_3$) 1715 (acetate C=O) and 1695(C=O) cm^{-1}; NMR δ 0.71(18-CH_3), 1.13(19-CH_3), 1.98($OC(=O)CH_3$), 2.11(21-CH_3), and 5.25(broad, 11-CH).

3,3-Dimethoxy-11α-hydroxy-5β-pregnan-20-one 11-acetate(43).

The 3-keto compound 42(0.25 g, 0.67 mmoles) and 7 mg of p-toluenesulfonic acid were heated under reflux in methanol(10 ml) for

three hours. The solution was cooled in an ice-bath and the solid formed was filtered to give 43(0.208 g, 74 %). Recrystallization of the solid from hexane gave 43 as crystals, mp 128.5-131°; IR($CHCl_3$) 1715(acetate C=O), 1695(C=O), 1230(acetate C-O), and 1090(ketal C-O)-cm^{-1}; NMR δ0.67 (18-CH_3), 1.05(19-CH_3), 1.98(O$\overset{O}{\overset{\|}{C}}CH_3$), 2.10(21-$CH_3$), 3.15 and 3.24(6H of dimethyl ketal), and 5.14(broad, 11-CH).

3,3-Dimethoxy-5β-pregnane-11α,20β-diol 11-acetate(44).

The mono-ketone 43(1.38 g, 3.29 mmoles) was dissolved in 27 ml ethanol and treated with sodium borohydride(0.166 g). The reduction was carried out in a nitrogen atmosphere and the solution was continuously stirred. After 4.5 hours the reaction mixture was poured into ice-water and the product was extracted with methylene chloride. The extract was filtered through alumina and celite and the latter was washed with 100 ml of methylene chloride-hexane(1 : 3). The combined filtrates were concentrated and ligroin(35-60°) was added from time to time until no further solid was precipitated. After cooling overnight the solid precipitate was isolated by filtration and washed with ligroin(63-75°), producing 44(1.09 g, 73.6 %). One recrystallization from ligroin(63-75°) gave pure 20β-ol, mp 151.5-152°; IR($CHCl_3$) 3450(OH), 1715(acetate C=O), 1235(acetate C-O), and 1090(ketal C-O); NMR δ0.79 (18-CH_3), 1.05(19-CH_3), 1.11(doublet, J=6 Hz, 21-CH_3), 1.92(O$\overset{O}{\overset{\|}{C}}CH_3$), 3.12 and 3.20(6H of dimethyl ketal), 3.60(broad, 20-CH), and 5.05(broad, 11-CH).

3,3-Dimethoxy-5β-pregnane-11α,20β-diol 11-acetate, 20-nitrite ester(45).

The nitrite ester 45 was prepared in better than 90 % yield by the general method.

18-Oximino-11α,20β-dihydroxy-5β-pregnan-3-one 11-acetate(46).

a). From the nitrite ester 45. The nitrite ester 45(0.484 g, 1.07 mmoles) in 30 ml benzene was photolyzed for two hours according to the general procedure. Separation by silica gel(25 g) column chromatography gave 0.19 g(43.5 %) of the oxime 46 which was eluted by the solvent mixture, benzene : ether(the proportions ranged from 7 : 3 to 1 : 1). Crystallizations of the oxime from acetone-isopropyl ether and from ethyl acetate gave 46 having a wide mp range(100-120°), IR(KBr) 3420 (OH), 1715(acetate C=O), 1695(C=O), and 1240(acetate C-O) cm^{-1}; NMR δ1.07(19-CH_3), 1.20(doublet, J=6 Hz, 21-CH_3), 1.94(O$\overset{O}{C}CH_3$), 3.53(broad, 20-CH), 5.27(broad, 11CH), 7.35(medium broad, N=CH), and 9.03(broad, C=N-OH).

b). From the nitrite ester 48. The 3-keto nitrite ester 48(0.295 g, 0.73 mmoles) was dissolved in 30 ml benzene and photolyzed for 2.5 hours at room temperature according to the general procedure. The product after evaporation of solvent was treated with isopropyl alcohol and isolated by preparative TLC to give 0.133 g(45 %) of the oxime 46. The product also resisted purification by recrystallization as did the one prepared in a). IR and NMR data are the same as those of the oxime prepared in a).

11α,20β-Dihydroxy-5β-pregnan-3-one 11-acetate(47).

The 3,3-dimethoxy compound 44(0.423 g, 1 mmole) was refluxed for 30 minutes in acetone containing a few drops of dil. HCl. Upon dilution with water a precipitate(47; 0.359 g, 95 %) was formed and used for the next step without further purification(because of difficulties in

purifying this compound). NMR δ 0.82(18-CH_3), 1.10(doublet, J=6 Hz, 21-CH_3), 1.12(19-CH_3), 1.88(O$\overset{O}{C}CH_3$), 3.51(broad, 20-CH), and 5.12(broad, 11-CH).

11α,20β-Dihydroxy-5β-pregnan-3-one 11-acetate, 20-nitrite ester(48).

The nitrite ester 48 was prepared in 95 % yield from 47 according to the general method. NMR δ0.73(18-CH_3), 1.10(19-CH_3), 1.32(doublet, 21-CH_3), 1.90(O$\overset{O}{C}CH_3$), and 5.17(broad, 11- and 20-CH).

Pregn-5-ene-3β,20β-diol 3-acetate(50).

Sodium borohydride(15.6 g, 0.41 moles) was added to an ice-bath cooled methanol solution(650 ml) of pregnenolone acetate(49; 107.35 g, 0.3 moles) maintained in a nitrogen atmosphere. The temperature of the reaction was then permitted to rise to room temperature with stirring. After 1.8 hours the reaction mixture was poured into 20 % acetic acid solution(500 ml), diluted with water(1200 ml), and refrigerated for 1-2 hours. A precipitate formed was filtered, washed with water, and dried *in vacuo*. After one recrystallization from methanol, 83.95 g (77.7 %) of 50 was obtained sufficiently pure for use in the next reaction. Mp 159-162°(lit.[35,40b] mp 165-166.5°); NMR δ 0.77(18-CH_3), 1.03(19-CH_3), 1.14(doublet, J=6 Hz, 21-CH_3), 2.02(O$\overset{O}{C}CH_3$), 3.73(broad, 20-CH), 4.63(broad, 3-CH), and 5.25(broad, 6-CH).

Pregn-5-ene-3β,20β-diol 3-acetate, 20-nitrite ester(51).

The 20β-hydroxy compound 50(21.15 g, 58.8 mmoles) was suspended in pyridine(210 ml) and cooled in a dry ice-CCl_4 bath. Nitrosyl chloride was added until the solution became dark blue and the reaction mixture was then allowed to warm to room temperature. When all the steroid had

dissolved(30 minutes), water was added to quench the reaction. Workup according to the general method gave 21.7 g(95 %) of 51; NMR δ 0.68 (18-CH_3), 1.01(19-CH_3), 1.35(doublet, 21-CH_3), 2.02(O$\overset{O}{\overset{\|}{C}}CH_3$), 4.57(broad, 3-CH), 5.37(broad, 6-CH), and 5.50(broad, 20-CH).

18-Oximinopregn-5-ene-3β,20β-diol 3-acetate(52).

The nitrite ester 51(6.8 g, 17.5 mmoles) in dry benzene(550 ml) was photolyzed for 4.3 hours according to the general method. Upon completion of the photolysis, the solution was concentrated to approximately 10 ml and chromatographed. Elution from alumina(315 g) with benzene, benzene-ether(the ratios ranged from 9 : 1 to 3 : 1) and finally ether yielded pregnenolone acetate(49) and pregn-5-ene-3β,20β-diol 3 acetate(51). The more polar 18-oximino compound was eluted with ether-methanol(19 : 1). After evaporation of the eluant, 1.78 g(26.2 %) of 52 was obtained. An analytical sample was prepared by three recrystallizations of the oxime from ethanol. Mp 160-161°(lit.[10b] double mp 160-162° and 178-179°); IR($CHCl_3$) 3580 and 3310(OH), 1715(acetate C=O), and 1220(ester C-O) cm^{-1}; NMR δ 0.95(19-CH_3), 1.15(doublet, J=6 Hz, 21-CH_3), 2.03(O$\overset{O}{\overset{\|}{C}}CH_3$), 3.70(broad, 20-CH), 4.63(broad, 3-CH), 5.38 (broad, 6-CH), 7.50(18-CH), and 9.33(broad, C=N-OH).

Anal. Calcd for $C_{23}H_{35}N_1O_4$: C, 70.92; H, 9.06; N, 3.60. Found: C, 71.16; H, 9.09; N, 3.50.

18-Aminopregn-5-ene-3β,20β-diol(53).

The oxime 52(2.56 g, 6.6 mmoles) in dioxane(40 ml) was added to a suspension of lithium aluminum hydride(2.56 g) in dioxane(40 ml) and the reaction was refluxed for 3.6 hours. The excess lithium aluminum hydride was destroyed with water(10 ml). The white precipitated solid

was removed by filtration through alumina and washed with dioxane and chloroform. The combined filtrates were then concentrated with addition of methanol until virtually all dioxane and chloroform had been replaced by methanol. After cooling the precipitate was filtered, giving 53(1.9 g, 86.5 %). Mp 244.5-246°(lit.[10b] mp 246-248°); IR(KBr) 3330(NH and OH) and 1435 and 1050(C-N) cm^{-1}; m/e 333(M^+).

18-Aminopregn-5-ene-3β,20β-diol 18-N-isopropylidene derivative(54).

The 18-amino steroid 53(1.67 g, 5.0 mmoles) was recrystallized from acetone to give the isopropylidene derivative 54(1.78 g, 95 %), mp 244-246°(lit.[10b] mp 247-249°); IR($CHCl_3$) 3600 and 3210(OH) and 1668 (C=N) cm^{-1}; NMR δ 0.99(19-CH_3), 1.14(doublet, J=6 Hz, 21-CH_3), 1.87 and 2.04(two olefinic methyl groups), 3.51(broad, 20-CH), 4.43(broad, 3-CH) and 5.42(broad, 6-CH); m/e 373(M^+).

18-Aminopregn-5-ene-3β,20β-diol 18-N-(α-chloroacetate)(55).

a). Conversion of the amine 53 to the α-chloroamide 55 with α-chloroacetyl chloride.

Sodium hydroxide(14 g, 1 % solution) was added over a 15 minute period to a cooled(-10 to -2°) solution of the amine(53; 0.17 g, 0.52 mmoles) and chloroacetyl chloride(0.17 g, 1.5 mmoles) in chloroform (15 ml) with vigorous stirring. The reaction mixture was then stirred for a further hour at -10 to -2° and subsequently for 20 minutes at 5 to 10°. After dilution with ethyl acetate the separated organic layer was washed with dil. HCl solution, water, $NaHCO_3$ solution and again with water. The dried solution was evaporated and the residue was recrystallized from ethyl acetate to give 0.144 g(68 %) of 55, mp 245-

246.5°; IR(KBr) 3250(NH), 1650(amide C=O), and 1540(amide band II) cm^{-1}.

Anal. Calcd for $C_{23}H_{36}Cl_1N_1O_3$: C, 67.38; H, 8.85; Cl, 8.65; N, 3.42. Found: C, 67.27; H, 8.95; Cl, 8.70; N, 3.29.

M/e 409:411, 3:1; M^+-H_2O; M^+-Cl; M^+-HCl; $M^+-ClCH_2CONH_2$.

The same product(55) was prepared(in ca. 40 % yield) by employing pyridine instead of the sodium hydroxide solution. Reaction conditions were identical with those above with the exception that stirring of the acylating mixture was continued at 0° overnight.

b). Conversion of the amine 53 to the α-chloroamide 55 with α-chloroacetic anhydride.

A methanolic solution(10 ml) of the 18-amine 53(0.167 g, 0.5 mmoles) and chloroacetic anhydride(0.34 g, 2.0 mmoles) was stirred 4 hours and maintained overnight at room temperature. After evaporation of solvent the residue was triturated with ether and the solid formed was washed with ether, producing 96 mg(47 %) of 55. The physical data were identical with those reported for the 55 above.

3-Hydroxymethyl-5,6-dihydro-γ-pyrone-carboxylic acid-2 Lactone(57).

The title compound was prepared by the method of Puetzer, et al.[108] with an overall yield of 13.7 % based on methyl vinyl ketone. IR(KBr) 1755(lactone C=O) and 1650(α,β-unsaturated C=O) cm^{-1}; NMR δ 2.78 (triplet, J=6.5 Hz, $-\overset{O}{\overset{\|}{C}}CH_2C$), 4.82(triplet, J=6.5 Hz, OCH_2C), and 5.00 ($C=CCH_2O$).

Rearrangement of the γ-pyrone(57) to lactam(58).

Sodium azide(1.0 g, 15.4 mmoles) was added over a 10-20 minute

period at 0° to a stirred solution of the pyrone 57(1.54 g, 10 mmoles) dissolved in conc. H_2SO_4(5 ml). After stirring for 5 hours at room temperature, the mixture was poured onto ice and the precipitated solid was filtered and washed with water. Recrystallization from acetone gave 0.55 g(32.5 %) of the lactam 58, mp 224.5-226°; IR(KBr) 3410(broad), 3230, 3180, and 3040(NH), 1765(lactone C=O), and 1675(amide C=O) cm^{-1}; NMR(CD_6O) δ 3.68(multiplet, NCH_2C), 4.57(multiplet, OCH_2C), and 4.90 ($OCH_2C{=}C$); UV 265-305 nm with a peak at 300 nm; m/e 169(M^+).

Anal. Calcd for $C_7H_7N_1O_4$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.59; H, 4.12; N, 8.22.

3-Hydroxymethyl-5,6-dihydro-6,6-dimethyl-γ-pyrone-carboxylic acid-2 Lactone(60).

The title compound was prepared in 50 % yield according to the method described by Puetzer, et al.[108] NMR δ 1.58(6H of gem-dimethyl), 2.70($-\overset{O}{\overset{\|}{C}}CH_2C$), and 5.02($OCH_2C{=}C$); UV 280 nm.

Rearrangement of the γ-pyrone(60) to lactam(62).

The γ-pyrone 60(1.54 g, 8.5 mmoles) was treated as described for the preparation of the lactam 58. After recrystallization from methanol, 1.37 g(82 %) of 62 was obtained, mp 232.5-234.5°; IR(KBr) 3430, 3260, and 3220(NH), 1770(lactone C=O), and 1660(amide C=O); NMR δ 1.50(6H of gem-dimethyl), 3.44(doublet, J=5.5 Hz, NCH_2C), 5.02($OCH_2C{=}C$), and 7.05 (broad, NH); m/e 197(M^+); UV 232-275 nm with a peak at 272 nm.

Anal. Calcd for $C_9H_{11}N_1O_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.71; H, 5.59; N, 7.11.

Preparation of the lactam(62) from oxime(61, a and b).

The oximes(61a,b) were prepared by refluxing the γ-pyrone(60; 8.19 g, 45 mmoles) and $NH_2OH \cdot HCl$(6.3 g, 90 mmoles) in a 70 % aqueous ethanol solution(80 ml). After 4.5 hours the solution was concentrated and cooled, yielding 7.2 g(83 %) of the oxime(61, a and b), mp 218°(dec); IR(KBr) 3250(OH), 1725(lactone C=O), and 1635(C=N) cm^{-1}; NMR(CD_6O) δ1.40(6H of gem-dimethyl), 2.60 and 2.65(1:1, NCH_2C of b and a), and 5.02 and 5.28 (1:1, $OCH_2C{=}C$ of a and b). UV 257.5-305 nm with a peak at 295 nm.

Anal. Calcd for $C_9H_{11}N_1O_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.79; H, 5.62; N, 7.06.

The oxime 61(1.97 g, 10 mmoles) was converted to the lactam 62 with phosphorus pentachloride(3 g, 15 mmoles) in tetrahydrofuran. The solution turned to yellow-red and a solid material separated. After stirring for one hour at room temperature, the mixture was poured into cold water. The oily layer which appeared after concentration of the aqueous solution yielded crystals(0.493 g, 25 %) of 62 upon cooling. The physical data were identical with those of the lactam prepared by the reaction of hydrazoic acid with the γ-pyrone 60.

Attempted Diels-Alder reactions with the γ-pyrones(57 and 60) and the lactams(58 and 62).

The Diels-Alder reactions were carried out either in a sealed glass tube or in an open system(Table IX). The glass tube was cooled with liquid nitrogen and was then sealed under vacuum. After heating in an autoclave the tubes were opened at liquid nitrogen temperatures. The enophile was used in large excess with or without solvent.

Table IX. Attempted Diels-Alder Reactions.

Starting material	Enophile	Conditions	Result
62	butadiene	toluene, 100° for 6 h, *	62
"	"	" , 155° for 3 d, *	62
"	"	acetone, 90° for 1 d, *	62 and tar
"	"	" , 110° for 3 d, *	62 and tar
"	"	- , 70° for 3 d, *	62
"	2,3-dimethyl-butadiene	toluene, 2 drops of Cl_2CHCOH (O), 100° for 1 d, *	62
"	"	- , refluxing for 2 d	62
60	"	- , " for 2 d	60
"	"	- , 3 drops of Cl_2CHCOH (O), 150° for 3 d, *	60
"	butadiene	methanol, 85° for 1 d, *	60
"	"	ethanol, 3 drops of AcOH, few crystals of hydroquinone, 130° for 1 d, *	60
"	"	- , few drops of AcOH, 170 190° for 1 d, *	60 and tar
58	"	benzene, 105° for 2 d, *	58 and tar
"	"	- , 170° for 3 d, *	58 and tar
"	2,3-dimethyl-butadiene	toluene, refluxing for 1 d	58
57	"	" , " " 1 d	57
"	butadiene	ethanol, few drops of AcOH, few crystals of hydroquinone, 170° for 1 d, *	57

* Autoclave.

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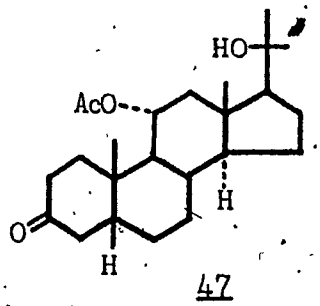
APPENDIX I

Calculation of Angular Methyl Protons Chemical Shifts.

The resonance frequency of angular methyl protons is dependent on both the nature and orientation of substituent groups in various locations of the steroid skeleton and moreover the frequency shifts of angular methyl protons induced by several different functional groups are additive. This additivity of chemical shifts was utilized for this calculation.

For the calculation of 11α,20β-dihydroxy-5β-pregnan-3-one 11-acetate



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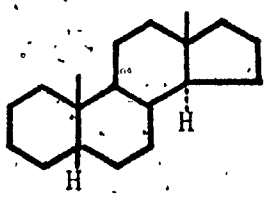


5β,14α-Androstane

Fig. XVI

Table X. Calculation Method of Angular Methyl Protons Chemical Shifts of Compound 47.

	18-CH_3	19-CH_3
5β,14α-Androstane	41.5	55.5
3-Oxo(5β)	2.5	7.0
11α-OAc	3.5	5.5
17β-CH(β-OH)CH_3	2.5	-0.5
11α,20β-Dihydroxy-5β-pregnan-3-one 11-acetate(47)	50.0	67.5

(47), for example, 5β,14α-androstane(Fig. XVI) having the unsubstituted steroid skeleton of compound 47 is taken as reference and the shifts for the various groups are obtained from Table XI and added to the 18- and 19-methyl resonances of the androstane(Table X).

Table XI. The Effect of Substituents on the Chemical Shift of 18- and 19-Methyl Protons at 60 MHz.

	18-CH_3	19-CH_3
5α,14α-Androstane	41.5	47.5
5β,14α-Androstane	41.5	55.5
3-Oxo(5α)	2.5	14.5
3-Oxo(5β)	2.5	7.0
3-Ethylene ketal(5β)*	-	2.0
11α-OAc	3.5	5.5
17α-$COCH_3$	12.0	0.5
17β-$COCH_3$	-5.0	-0.5
17β-CH(α-OH)CH_3	-3.0	-0.5
17β-CH(β-OH)CH_3	2.5	-0.5
17β-CH(α-OAc)CH_3	-2.0	-0.5
17β-CH(β-OAc)CH_3	-5.0	-0.5

* For the calculation of methyl resonances of the 3,3-dimethyl ketal of the 5β-series and 3-ethylene and 3,3-dimethyl ketal of 5α-series, this value was used in this work. These calculated results were in good agreement with observed data.

APPENDIX II

NMR Spectra.

1. 17β-Hydroxy-5α-androstan-3-one cyclic 3-(ethylene acetal)(3).
2. 5α-Androstane-3,17-dione cyclic 3-(ethylene acetal)(4).
3. 5α-Pregn-cis-$\Delta^{17(20)}$-en-3-one cyclic 3-(ethylene actal)(5).
4. 20β-Hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(6).
5. 20β-Hydroxy-5α-pregnan-3-one(7).
6. 18-Oximino-20β-hydroxy-5α-pregnan-3-one(9a).
7. 21-Nor-cis-$\Delta^{17(20)}$-5α-pregnan-3-one cyclic 3-(ethylene acetal)(11).
8. 17β-Hydroxymethyl-5α-androstan-3-one cyclic 3-(ethylene acetal)(12).
9. 17β-Hydroxymethyl-5α-androstan-3-one cyclic 3-(ethylene acetal), 20-nitrite ester(13).
10. 20β-Hydroxy-5α-pregnan-3-one 20-acetate(16).
11. 20α-Hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(19a).
12. A mixture of 5α-pregn-trans-$\Delta^{17(20)}$-en-3-one cyclic 3-(ethylene acetal)(21a) and its cis-$\Delta^{17(20)}$-ene isomer(5).
    a) Prepared from the 20α-tosylate(20a).
    b) Prepared from the 20β-tosylate(20b).
13. 20β-Hydroxypregn-4-en-18-oic acid 18,20-Lactone(29, a and b).
14. 20β-Hydroxy-5β-pregnan-3-one(30).
15. 20β-Hydroxy-5β-pregnan-3-one cyclic 3-(ethylene acetal)(31).
16. 18-Oximino-20β-hydroxy-5β-pregnan-3-one(33a).
17. 18-Oximino-20β-hydroxy-5β-pregnan-3-one cyclic 3-(ethylene acetal) (33b).
18. 11α-Hydroxypregn-4-ene-3,20-dione 11-acetate(41).
19. 11α-Hydroxy-5β-pregnane-3,20-dione 11-acetate(42).

20. 3,3-Dimethoxy-11α-hydroxy-5β-pregnan-20-one 11-acetate(43).

21. 3,3-Dimethoxy-5β-pregnane-11α,20β-diol 11-acetate(44).

22. 18-Oximino-11α,20β-dihydroxy-5β-pregnan-3-one 11-acetate(46).

23. 11α,20β-Dihydroxy-5β-pregnan-3-one 11-acetate(47).

24. 11α,20β-Dihydroxy-5β-pregnan-3-one 11-acetate, 20-nitrite ester(48).

25. Pregn-5-ene-3β,20β-diol 3-acetate(50).

26. Pregn-5-ene-3β,20β-diol 3-acetate, 20-nitrite ester(51).

27. 18-Oximinopregn-5-ene-3β,20β-diol 3-acetate(52).

28. 18-Aminopregn-5-ene-3β,20β-diol(53).

29. 18-Aminopregn-5-ene-3β,20β-diol 18-N-isopropylidene derivative(54).

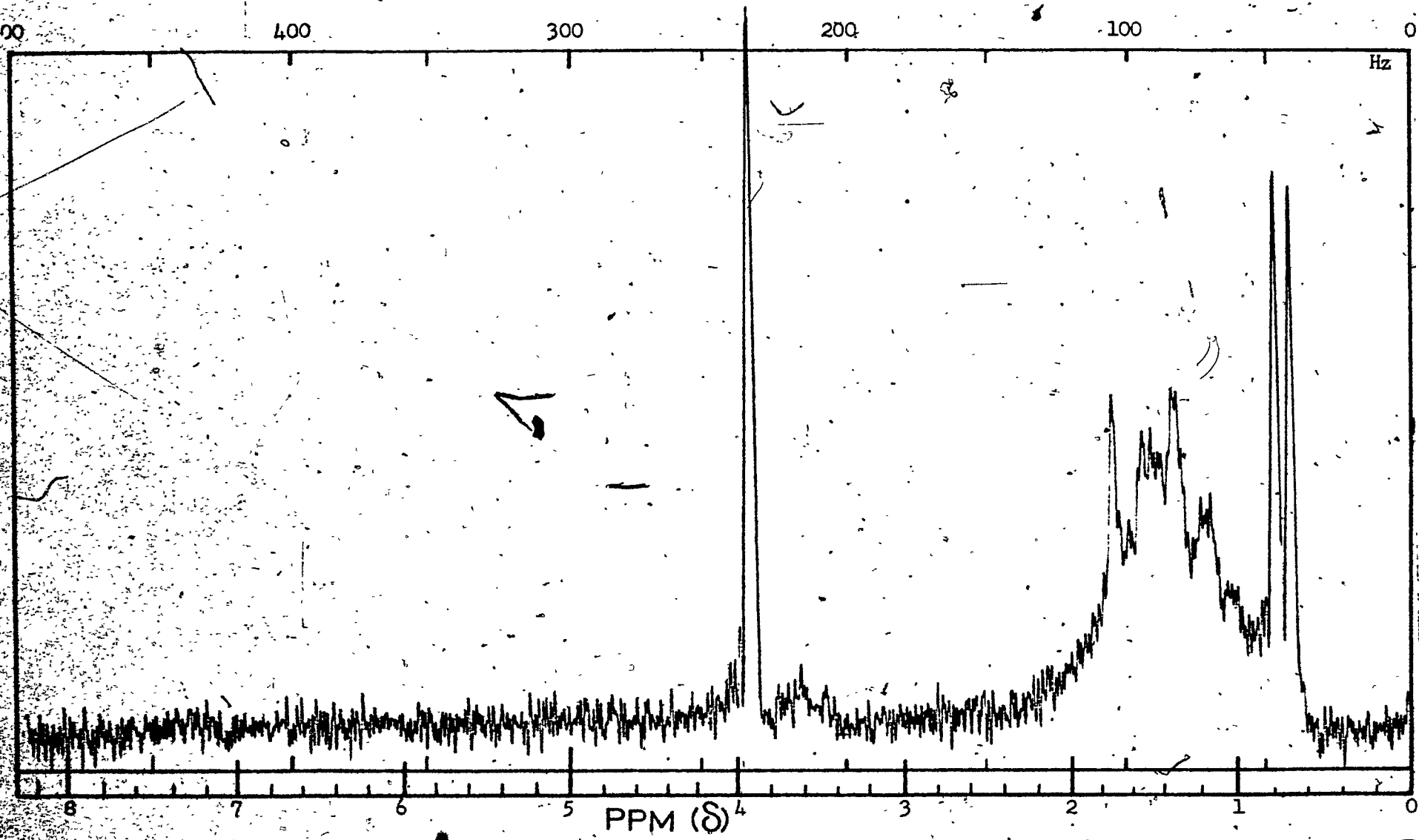
30. 3-Hydroxymethyl-5,6-dihydro-γ-pyrone-carboxylic acid-2 Lactone(57).

31. The lactam 58.

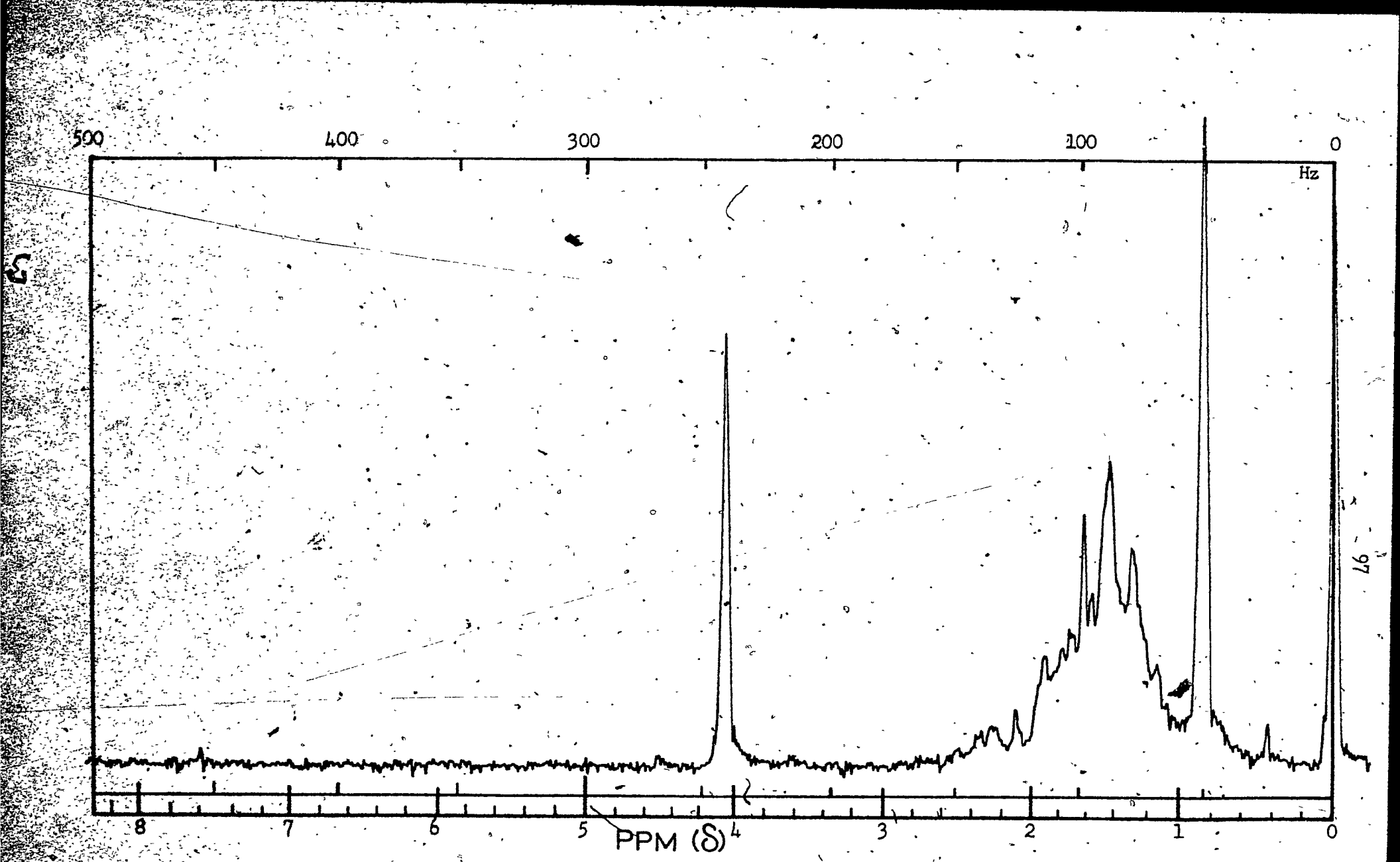
32. 3-Hydroxymethyl-5,6-dihydro-6,6-dimethyl-γ-pyrone-carboxylic acid-2 Lactone(60).

33. The oxime 61(a and b).

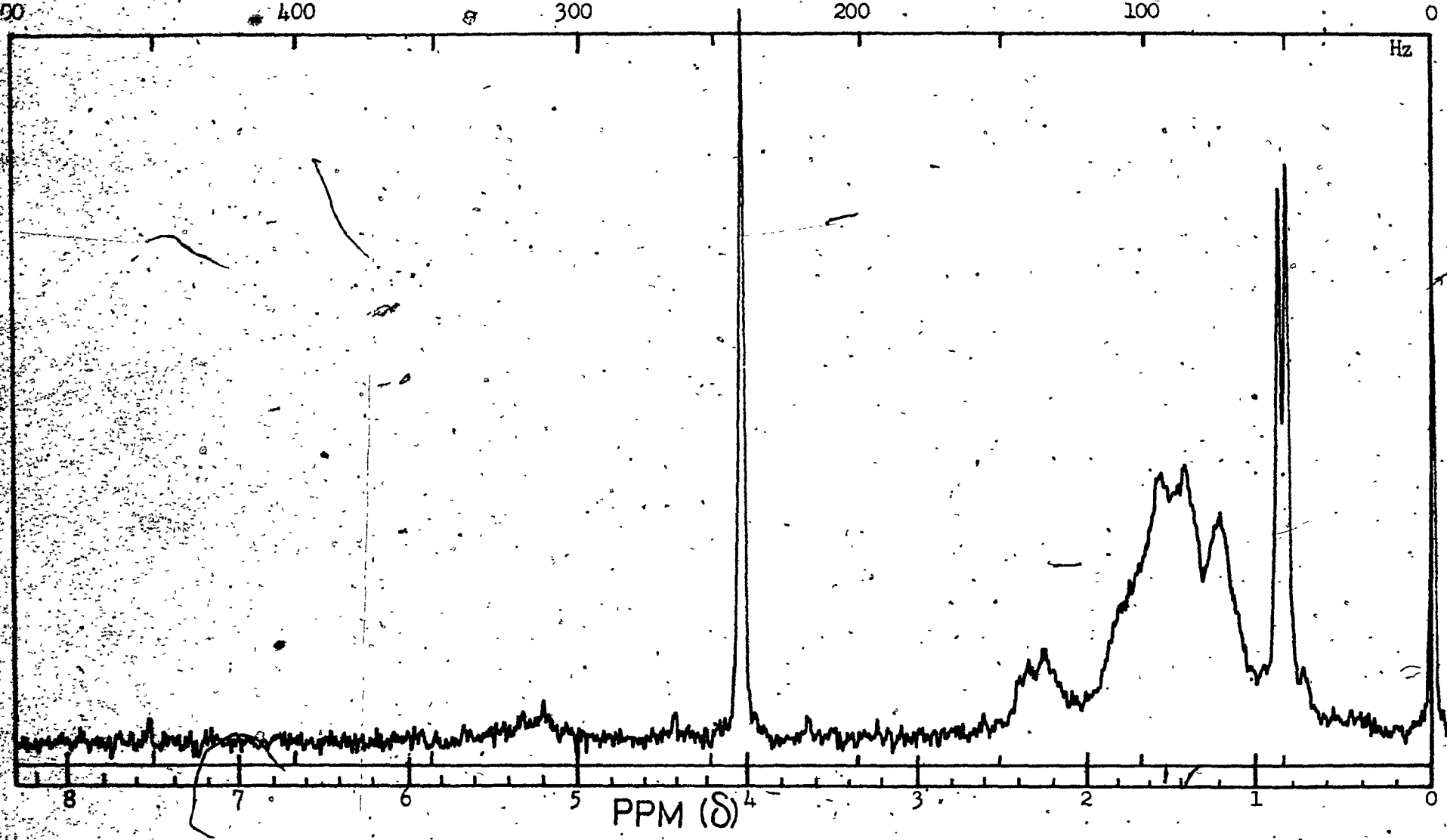
34. The lactam 62.



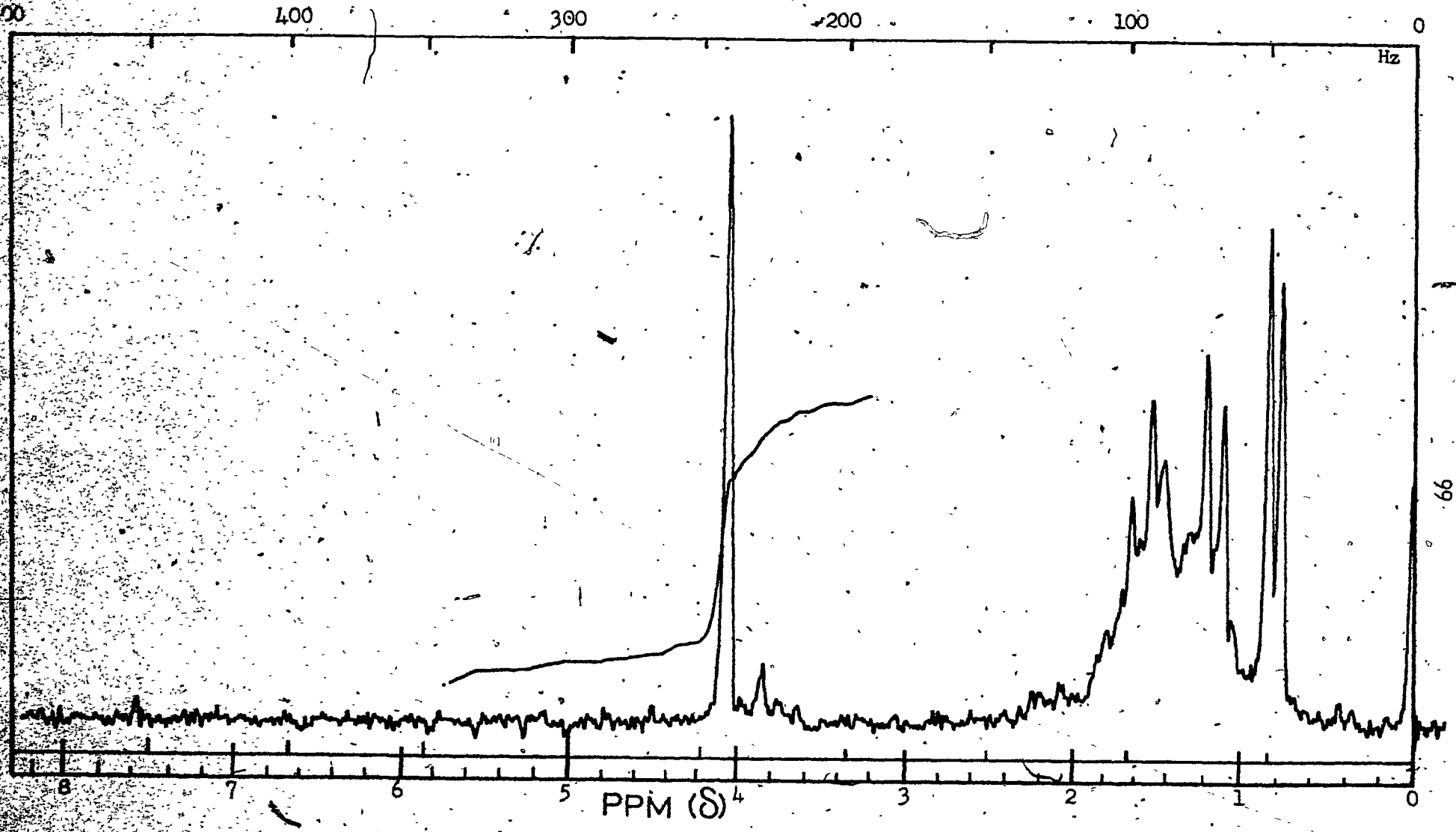
1. 17β-Hydroxy-5α-androstan-3-one cyclic 3-(ethylene acetal)(3).



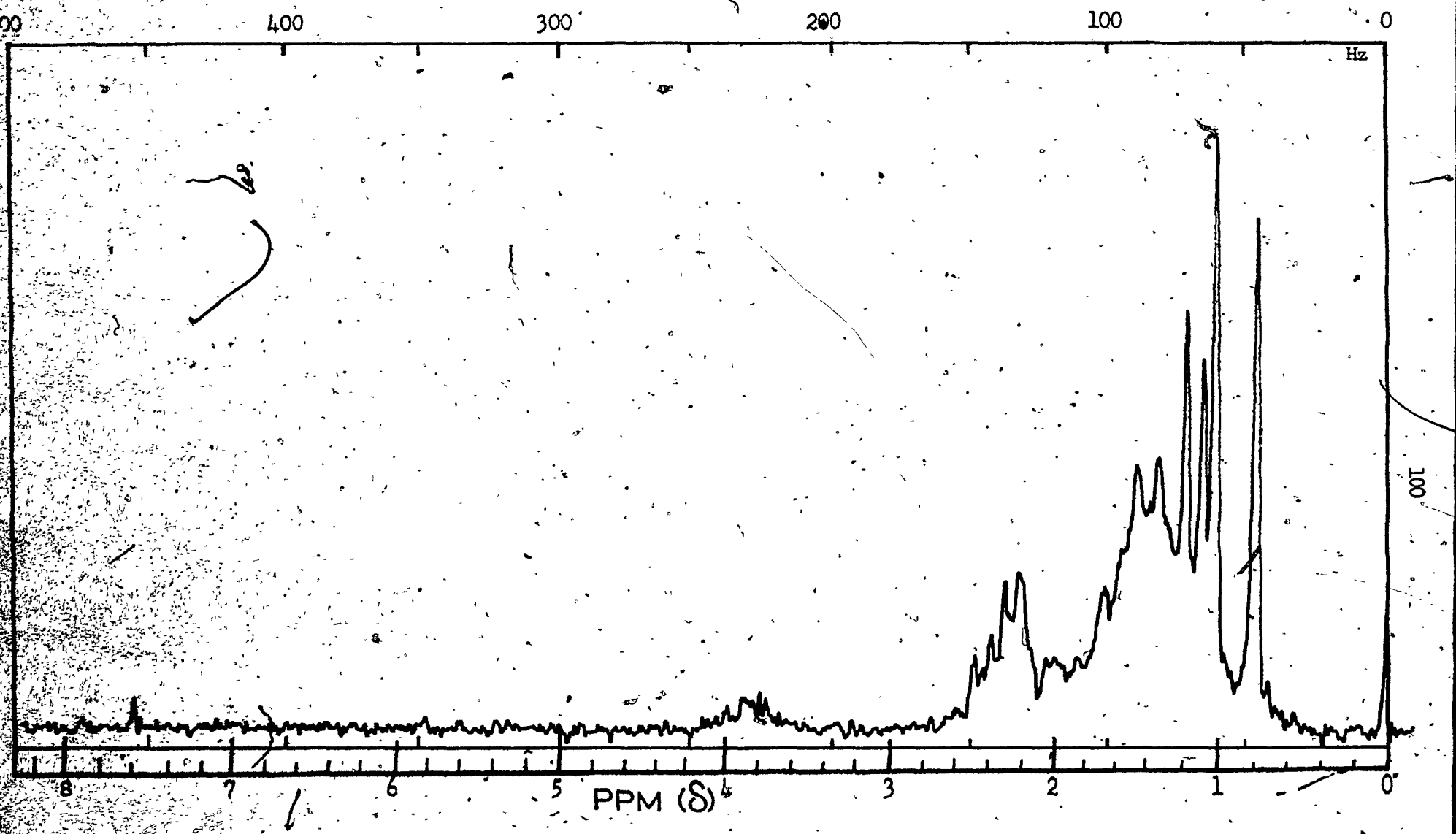
2. 5α-Androstane-3,17-dione cyclic 3-(ethylene acetal)(4).



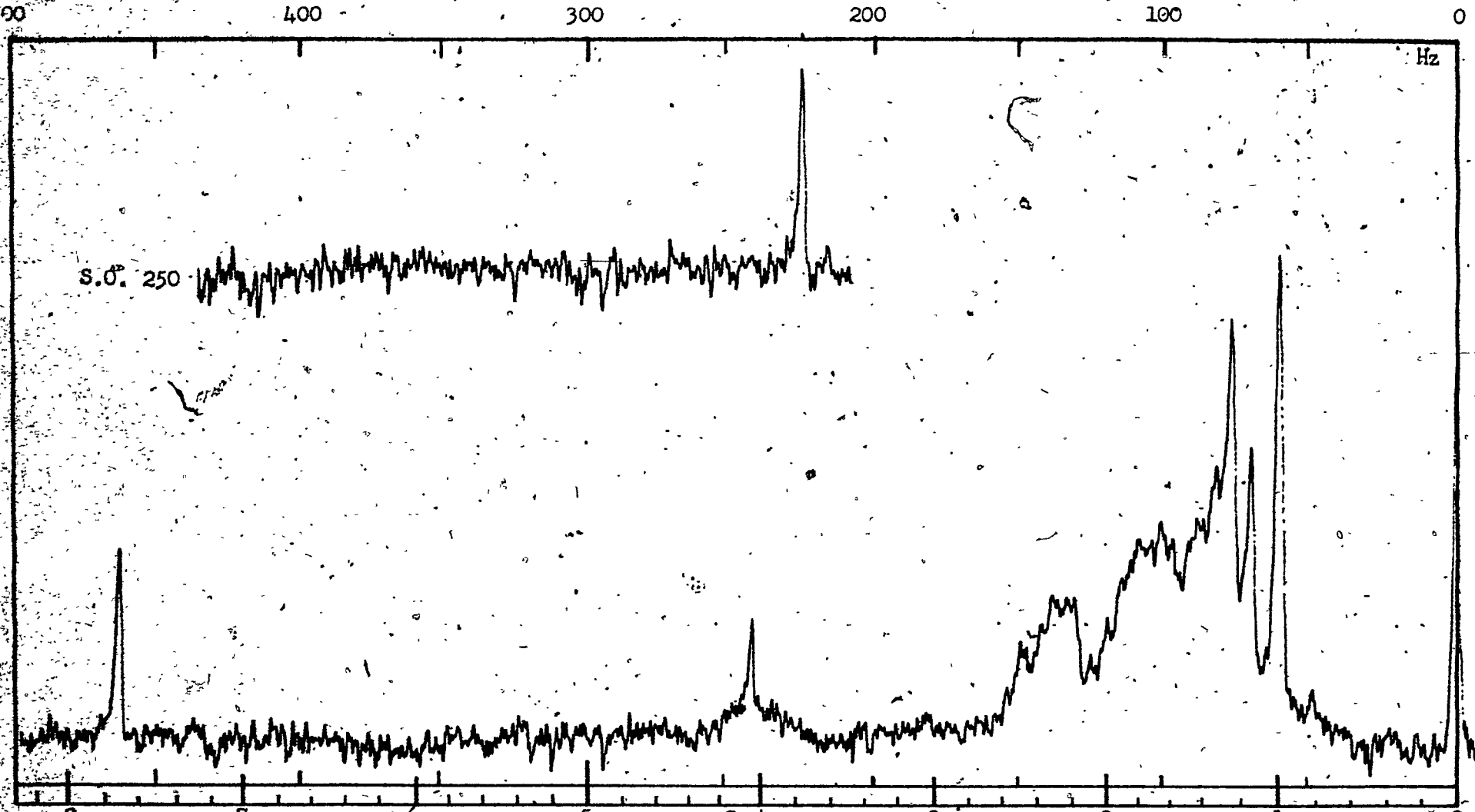
3. 5α-Pregn-cis-$\Delta^{17(20)}$-en-3-one cyclic 3-(ethylene acetal)(5).



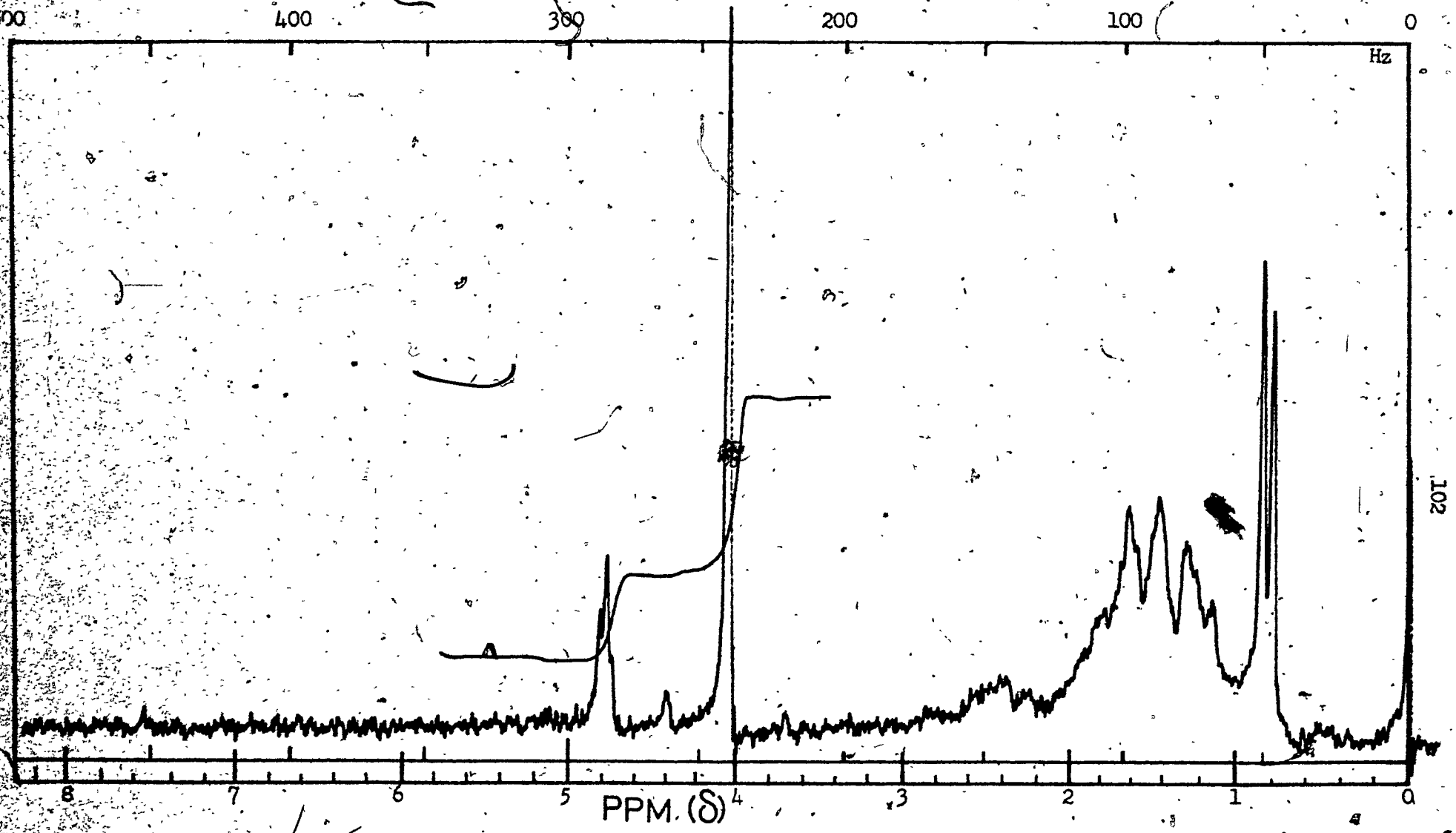
4. 20β-Hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(6).



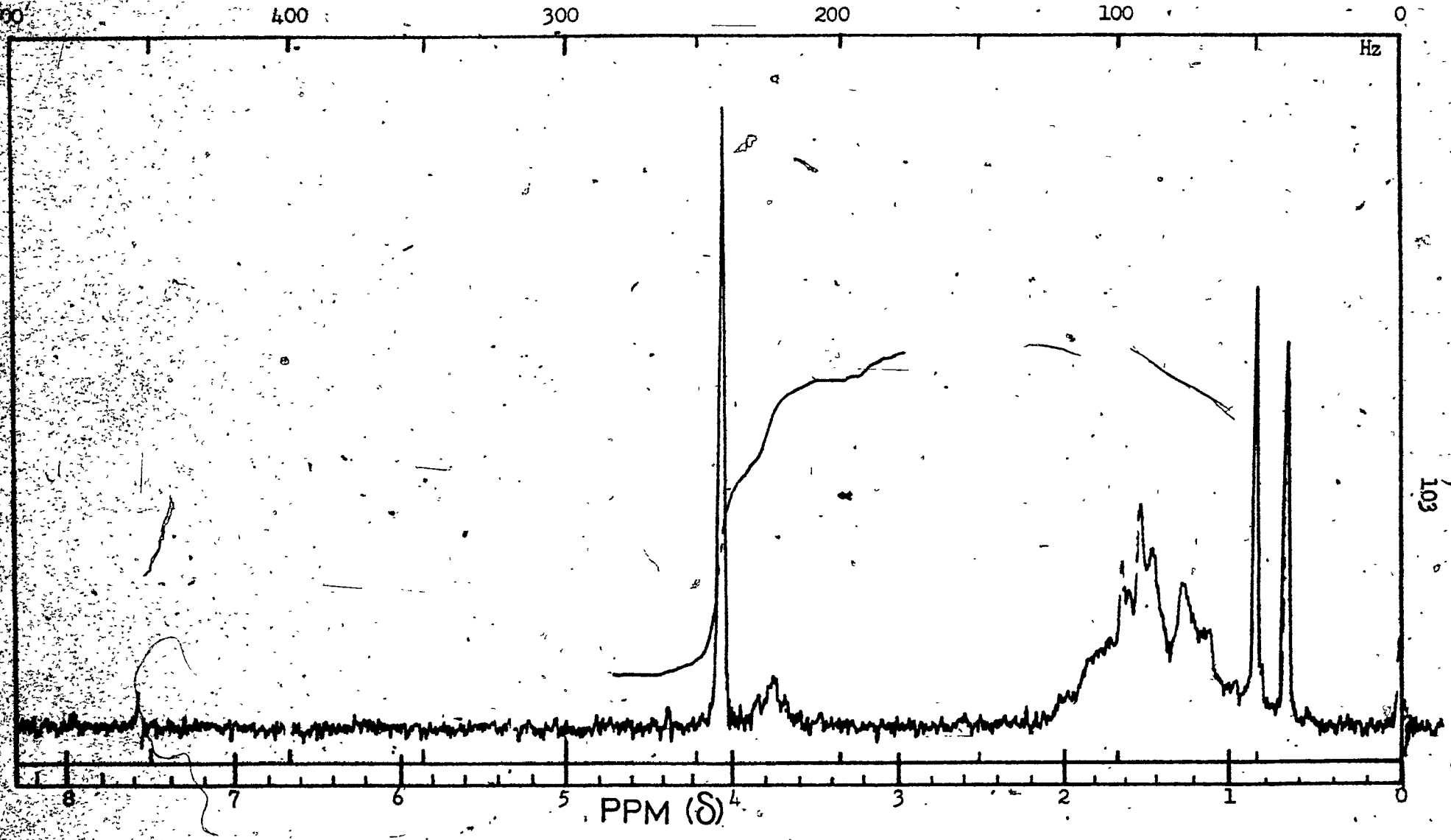
5. 20β-Hydroxy-5α-pregnan-3-one(7).



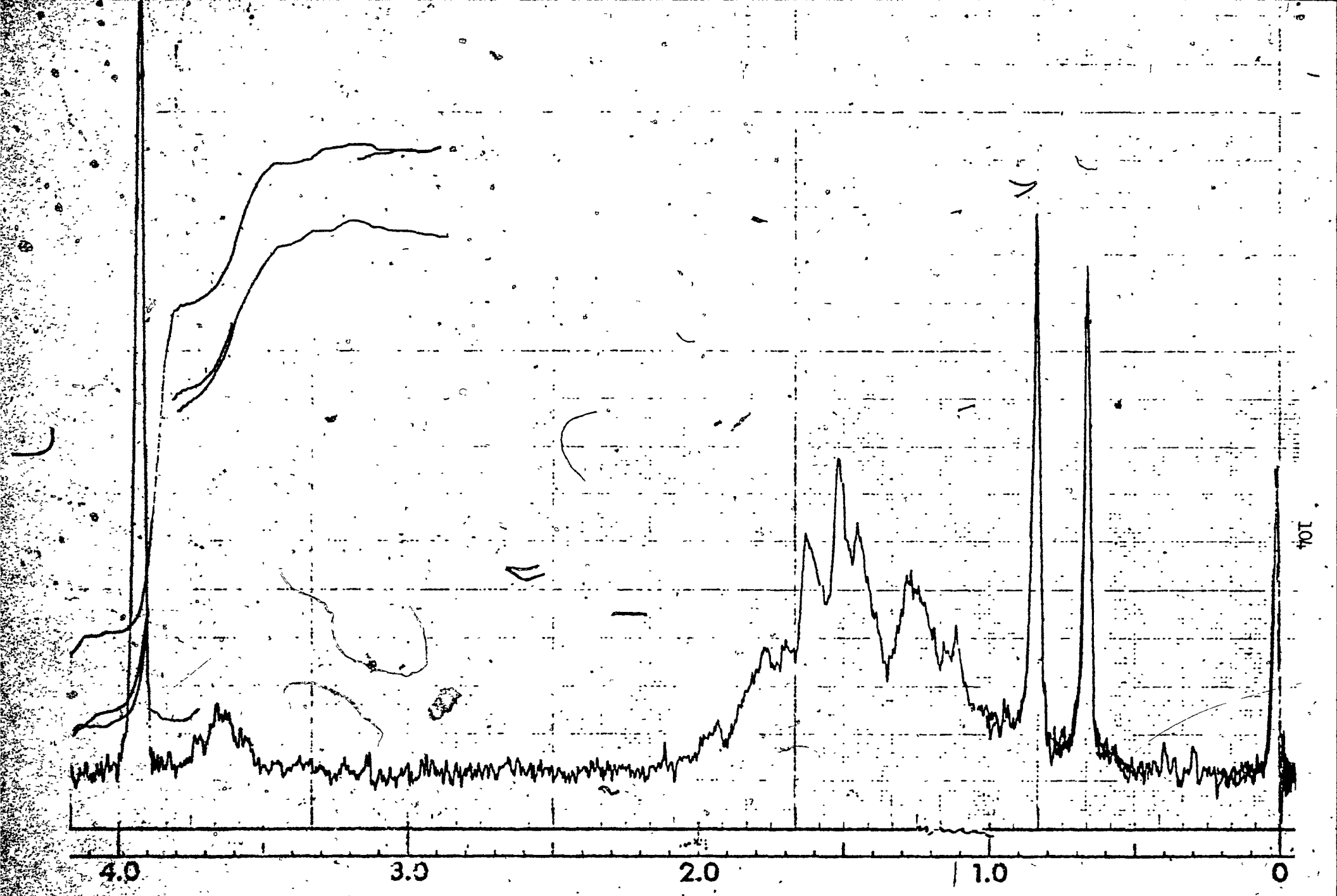
6. 18-Oximino-20β-hydroxy-5α-pregnan-3-one(9a).



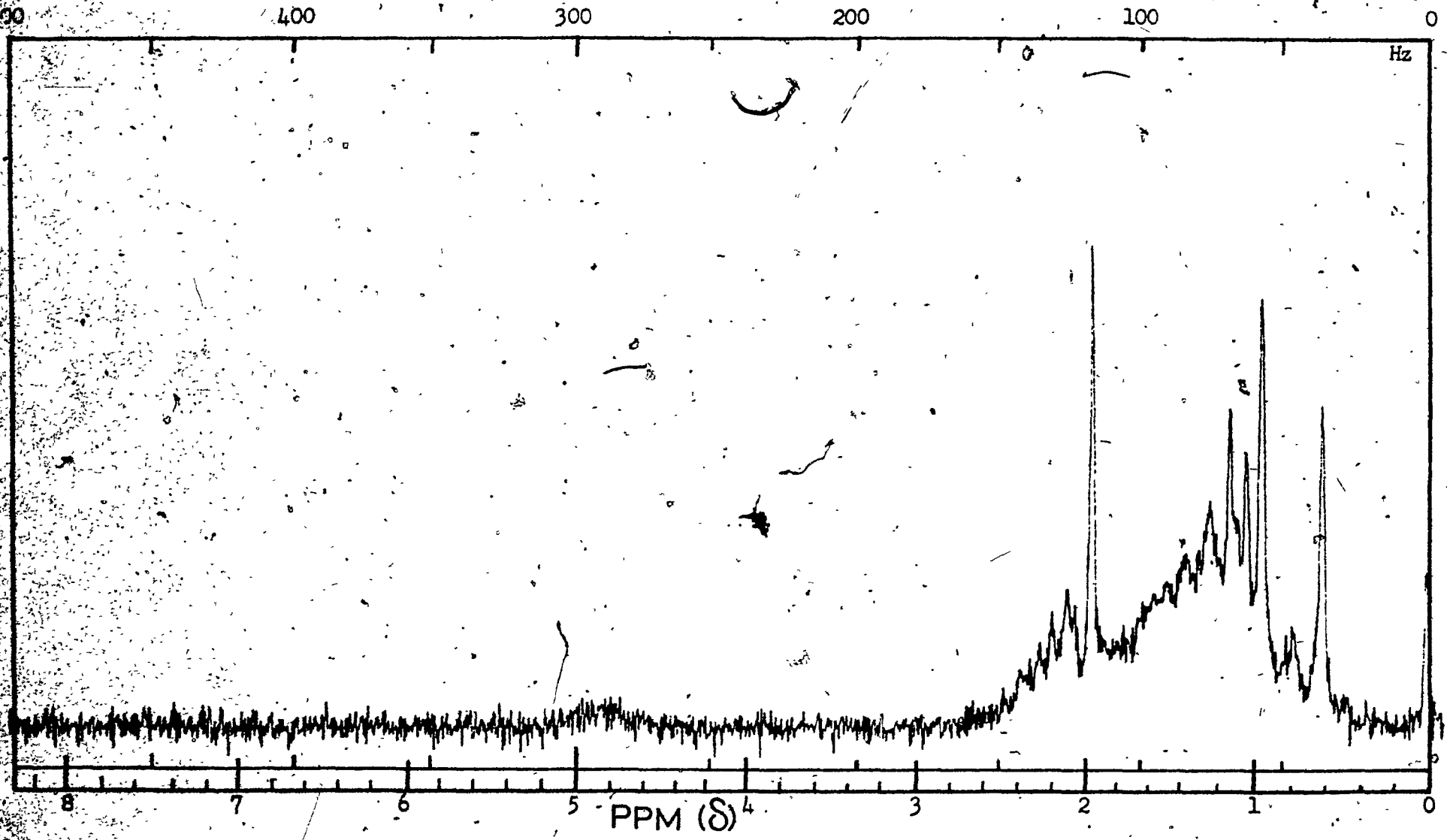
7. 22-Nor-cis-$\Delta^{17(20)}$-5α-pregnan-3-one cyclic 3-(ethylene acetal)(11).



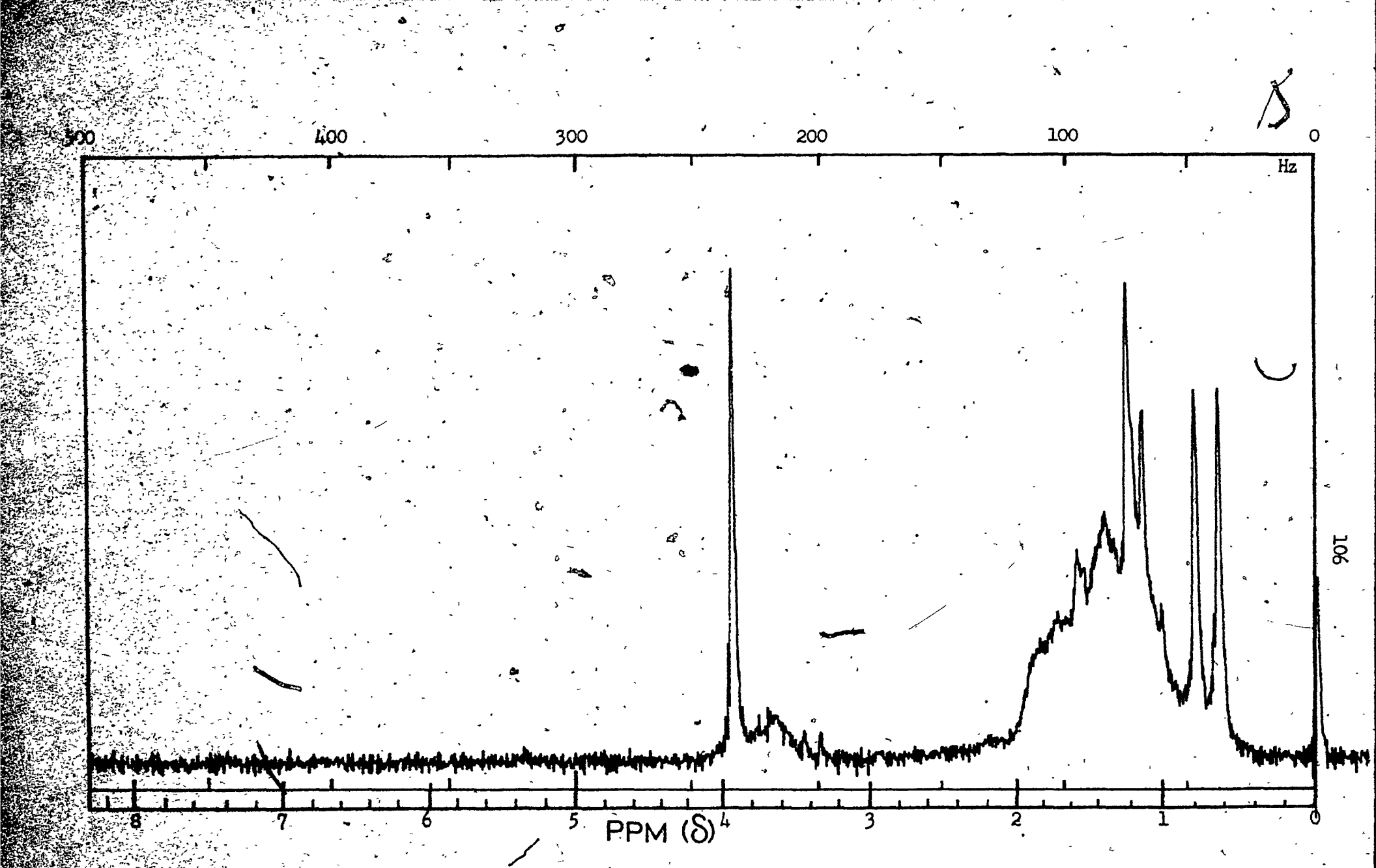
8. 17β-Hydroxymethyl-5α-androstan-3-one cyclic 3-(ethylene acetal)(12).



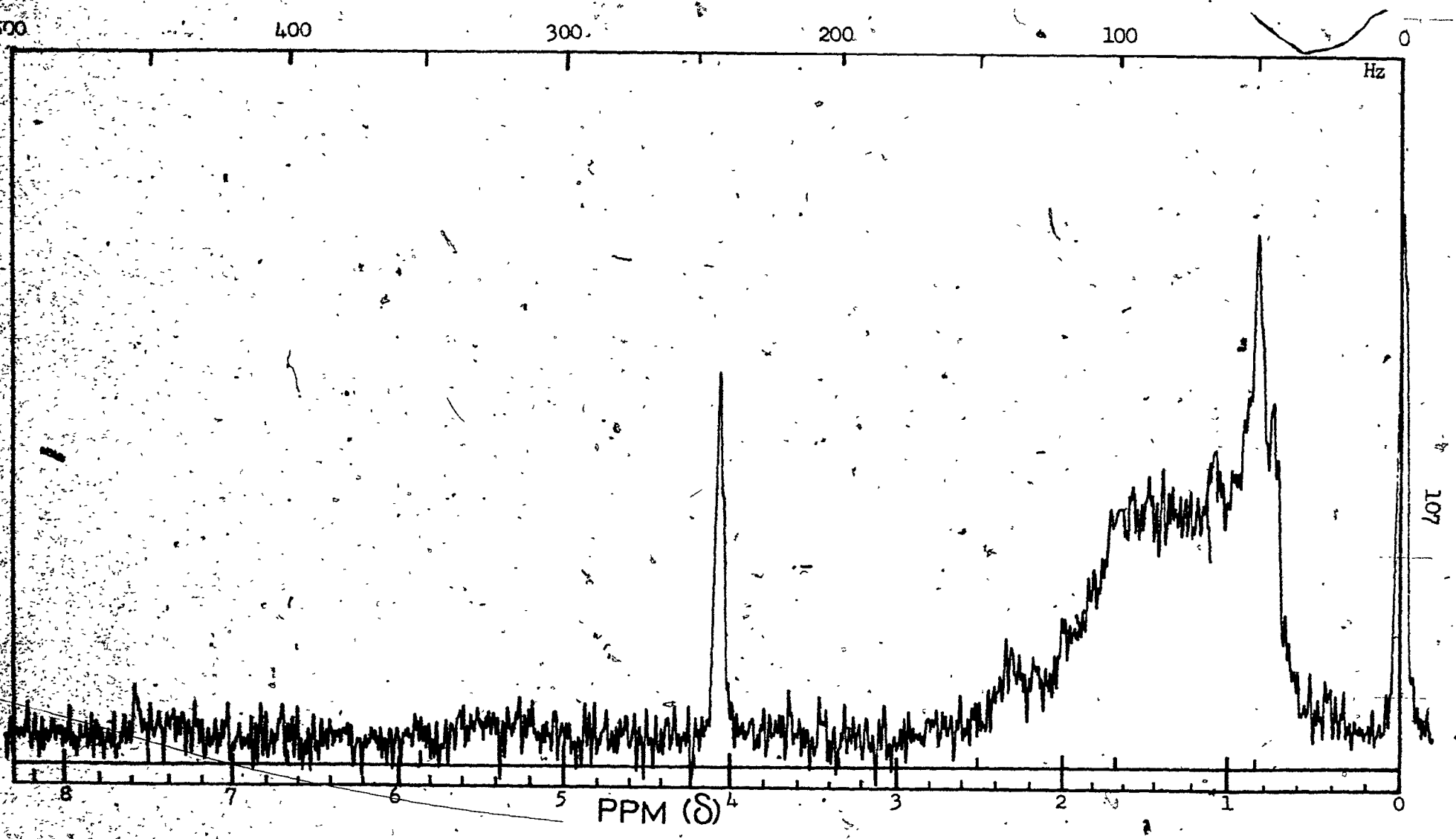
9. 17β-Hydroxymethyl-5α-androstan-3-one cyclic 3-(ethylene acetal), 20-nitrite ester(13).



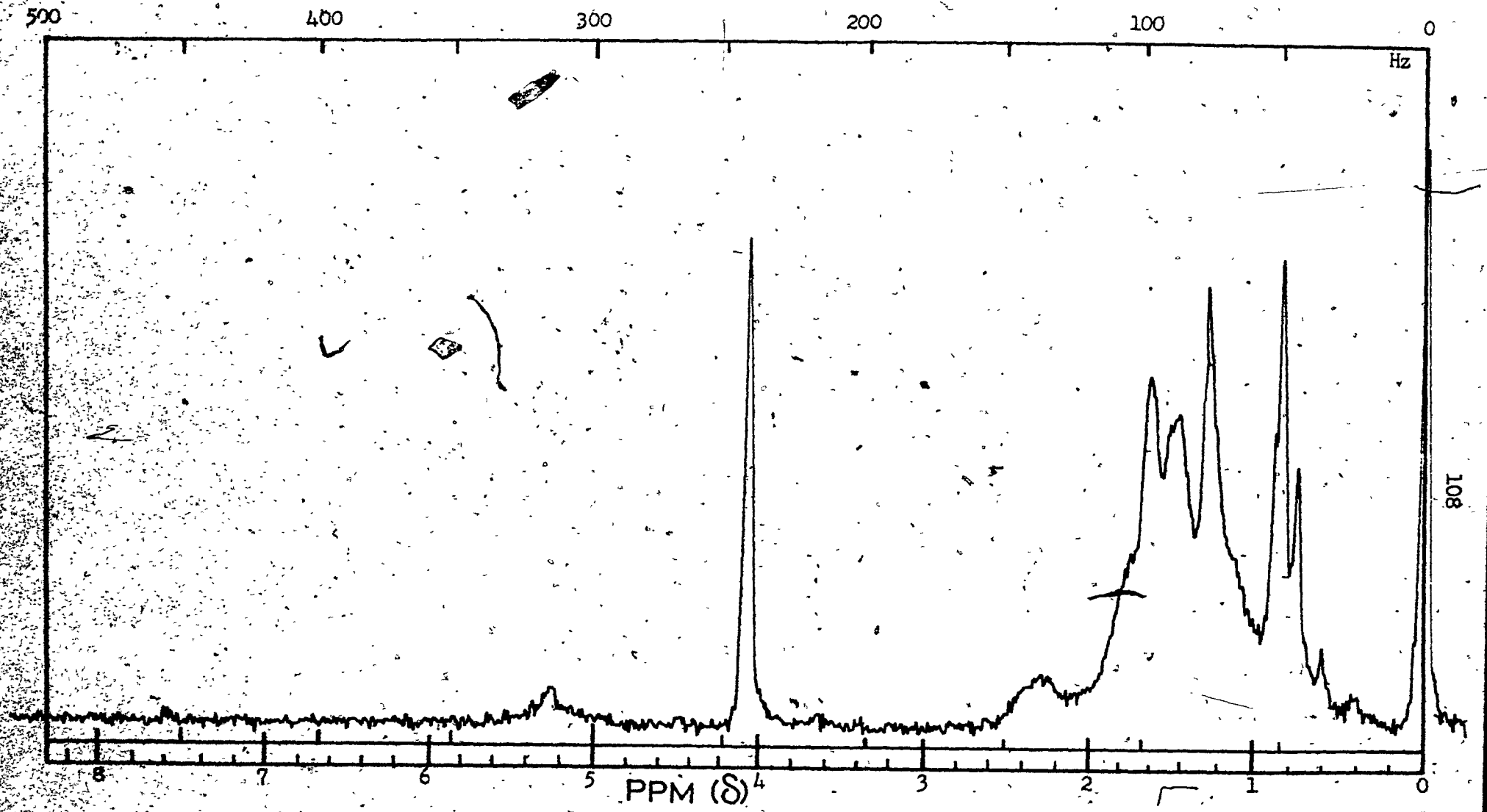
10. 20β-Hydroxy-5α-pregnan-3-one 20-acetate(16).



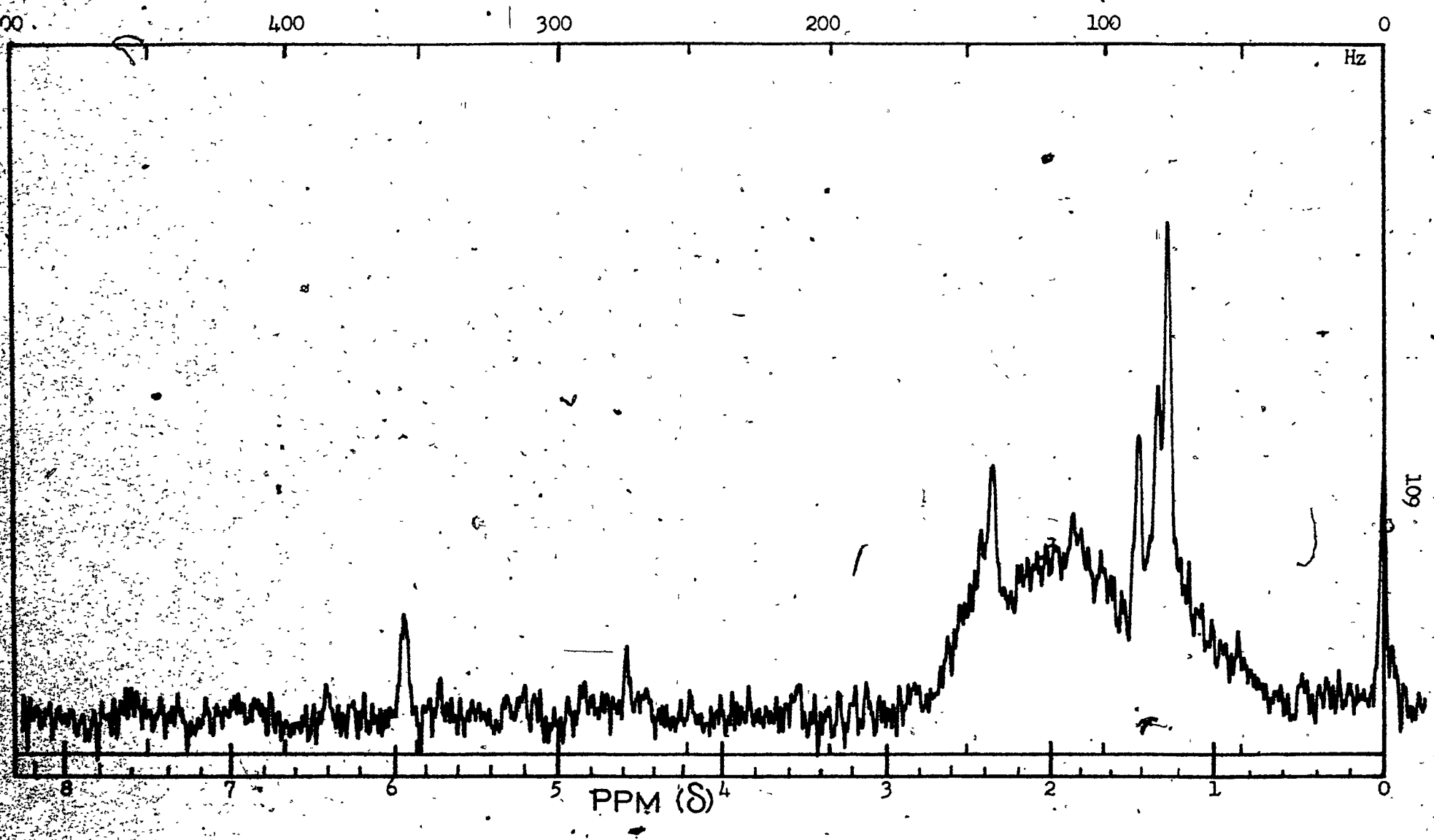
11. 20α-Hydroxy-5α-pregnan-3-one cyclic 3-(ethylene acetal)(19a).



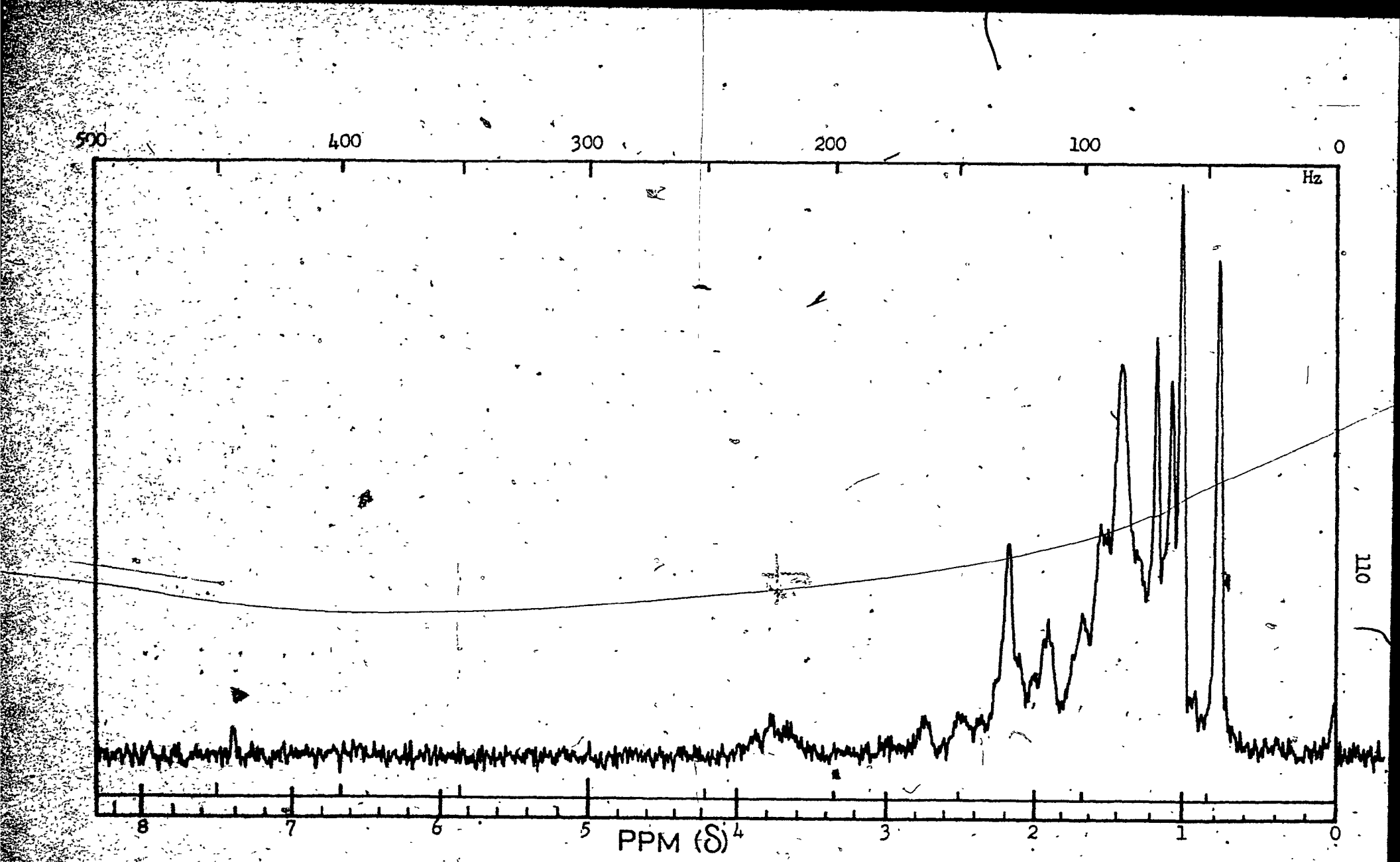
12, a) A mixture of 5α-pregn-trans-$\Delta^{17(20)}$-en-3-one cyclic 3-(ethylene acetal)(21a) and its cis-$\Delta^{17(20)}$-ene isomer(5) prepared from the 20α-tosylate(20a)



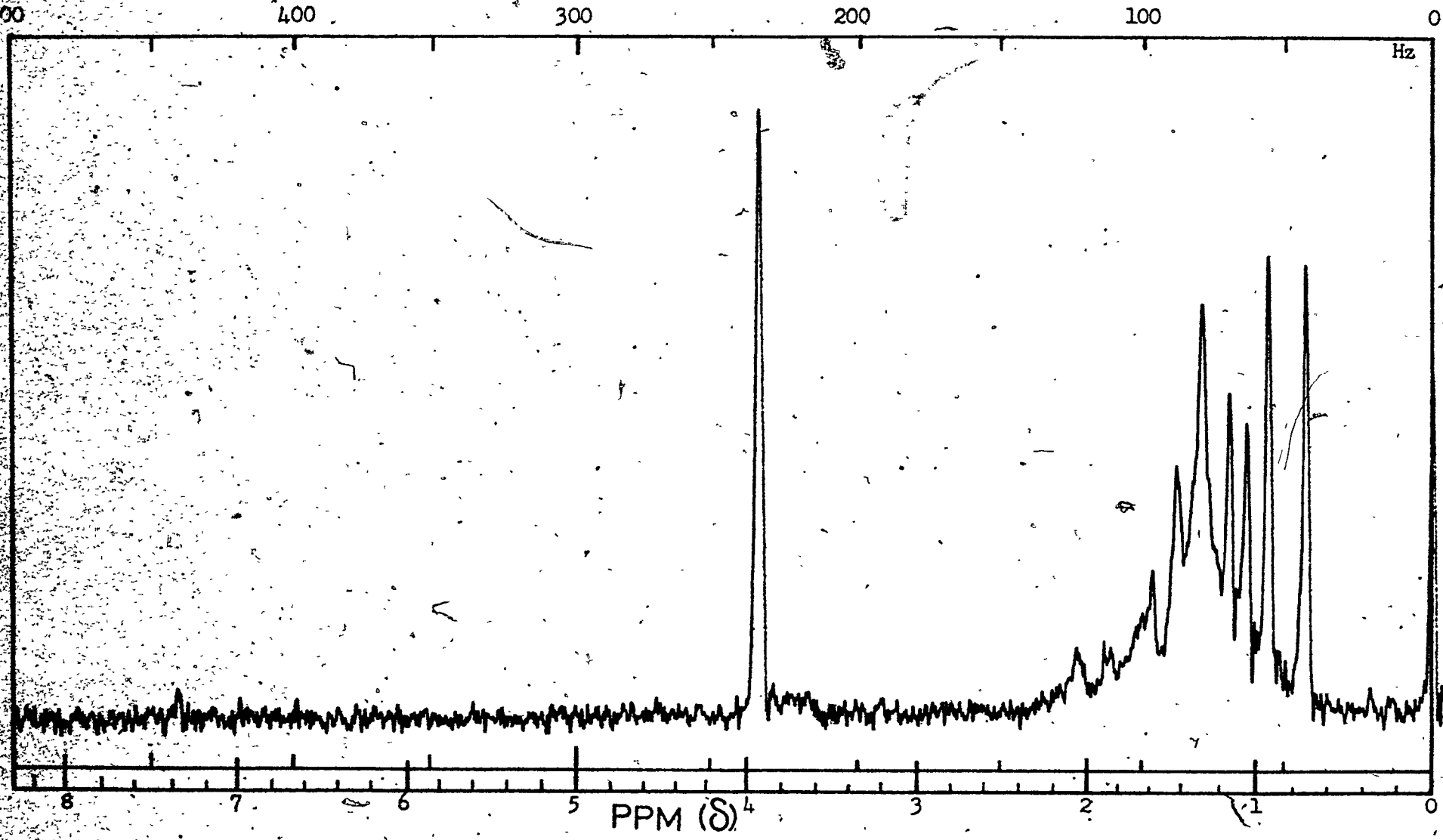
12, b) A mixture of 5α-pregn-trans-$\Delta^{17(20)}$-en-3-one cyclic 3-(ethylene acetal)(21a) and its cis-$\Delta^{17(20)}$-ene isomer(5) prepared from the 20ß-tosylate(20b).



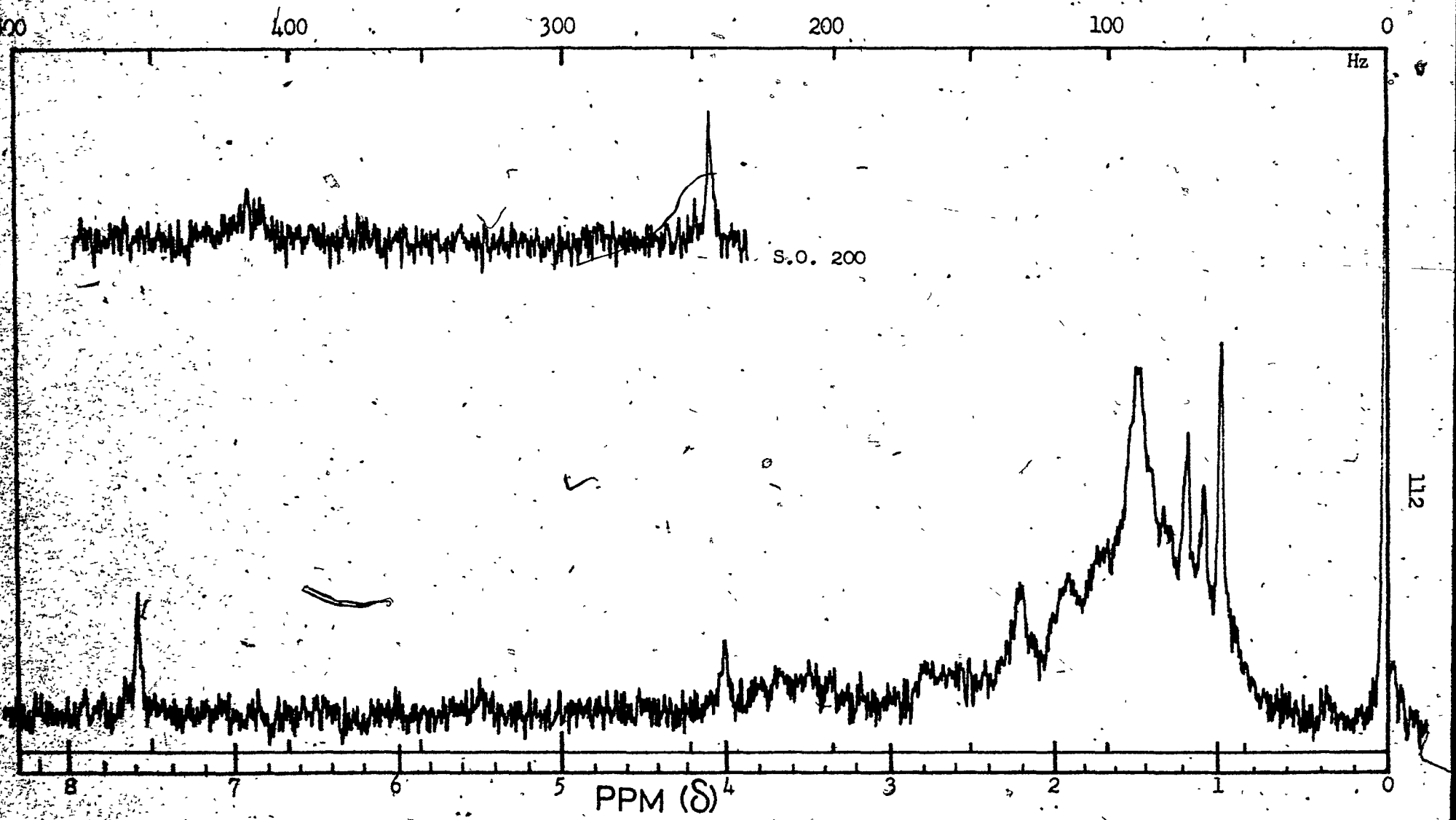
13. 20β-Hydroxypregn-4-en-18-oic acid 18,20-Lactone(29, a and b).



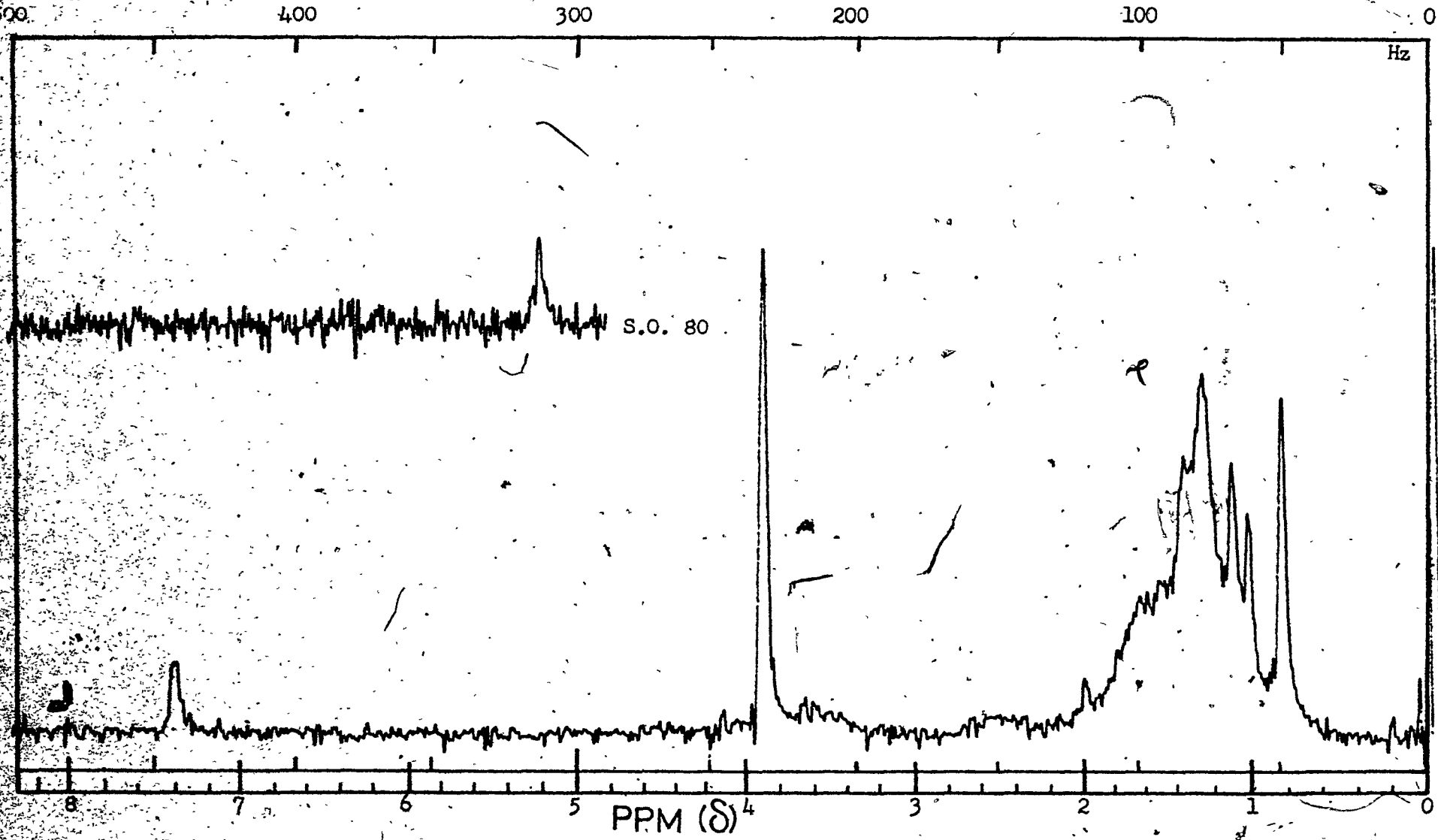
14. 20β-Hydroxy-5β-pregnan-3-one(30).



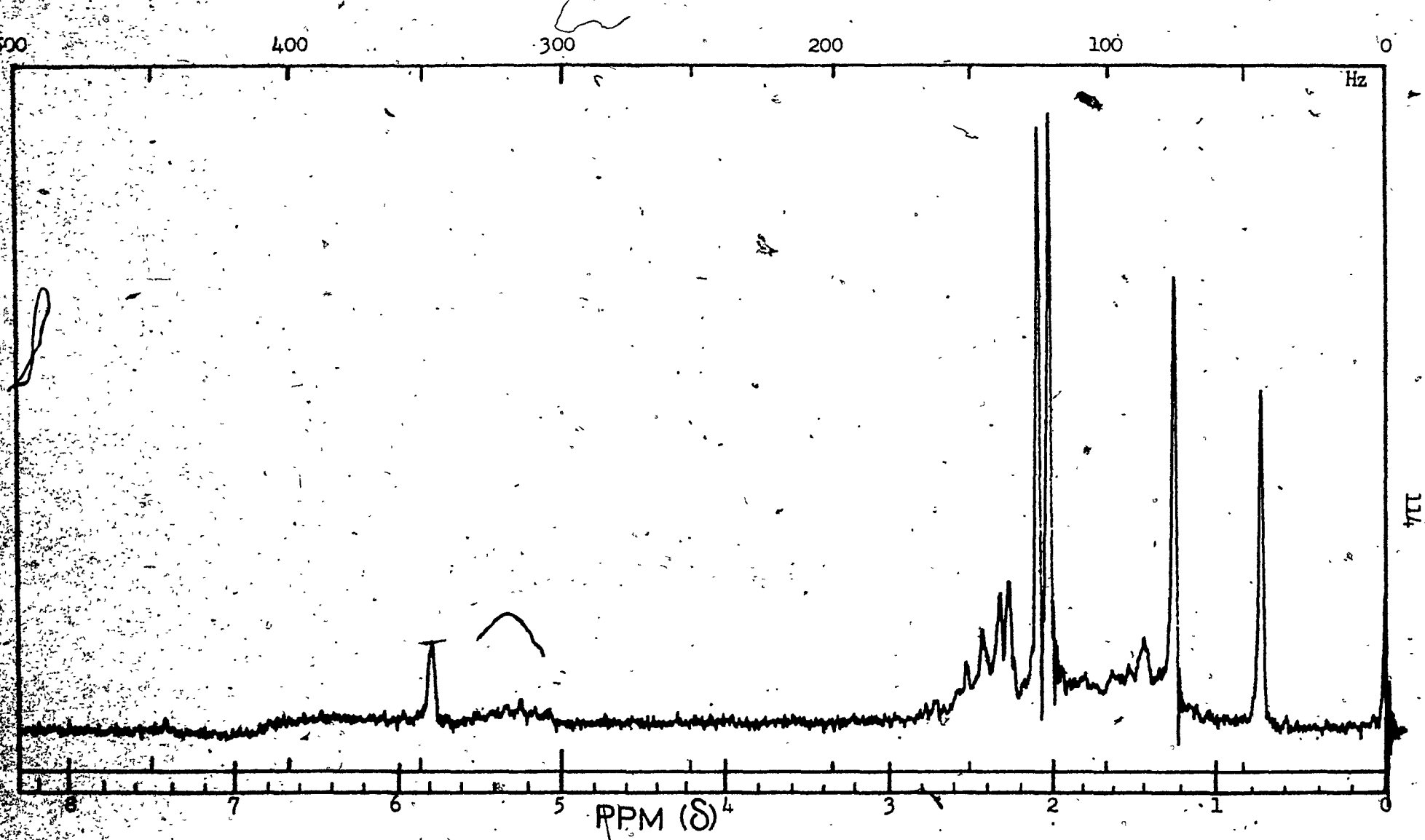
15. 20β-Hydroxy-5β-pregnan-3-one cyclic 3-(ethylene acetal)(31).



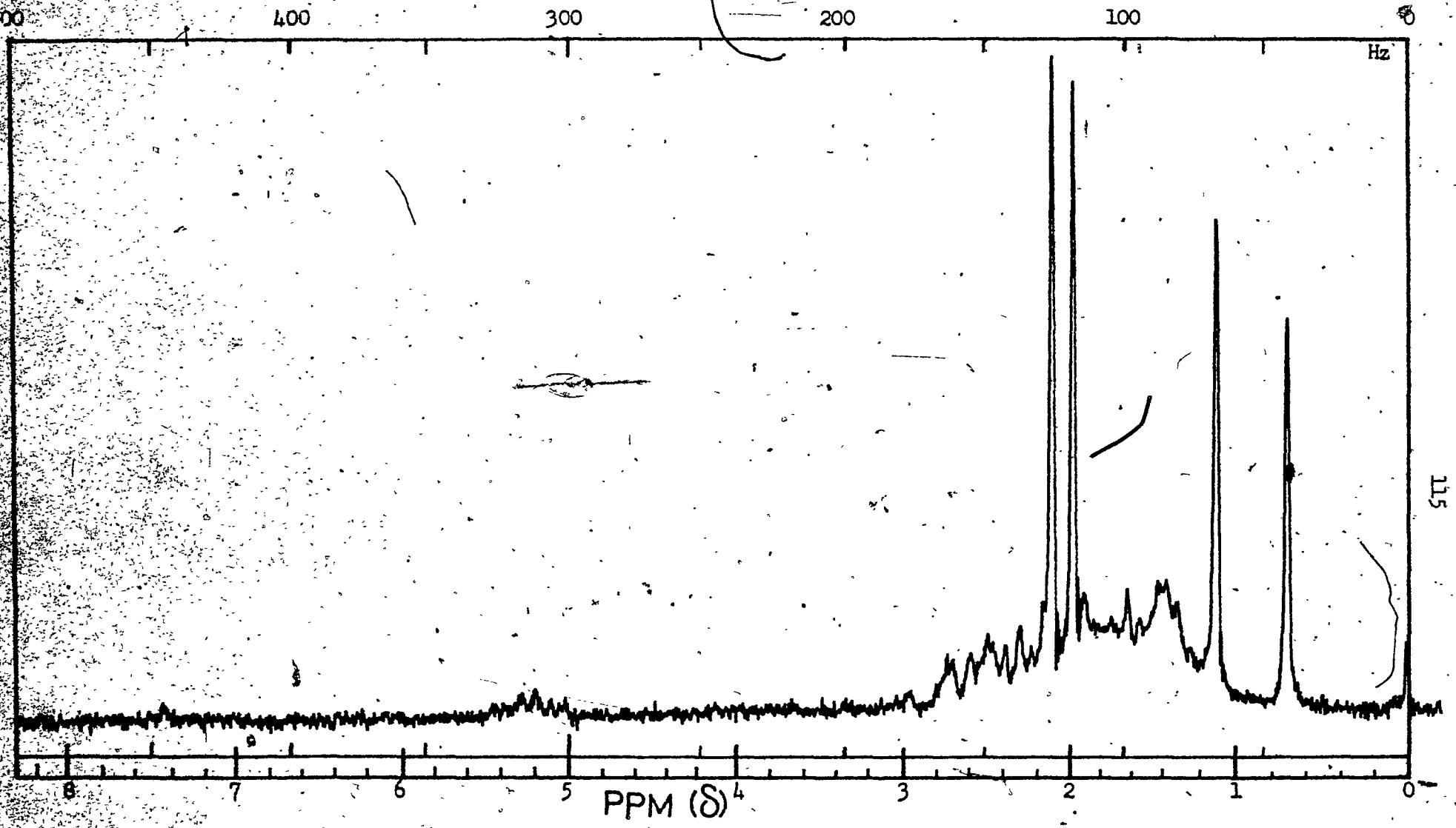
16. 18-Oximino-20β-hydroxy-5β-pregnan-3-one(33a).



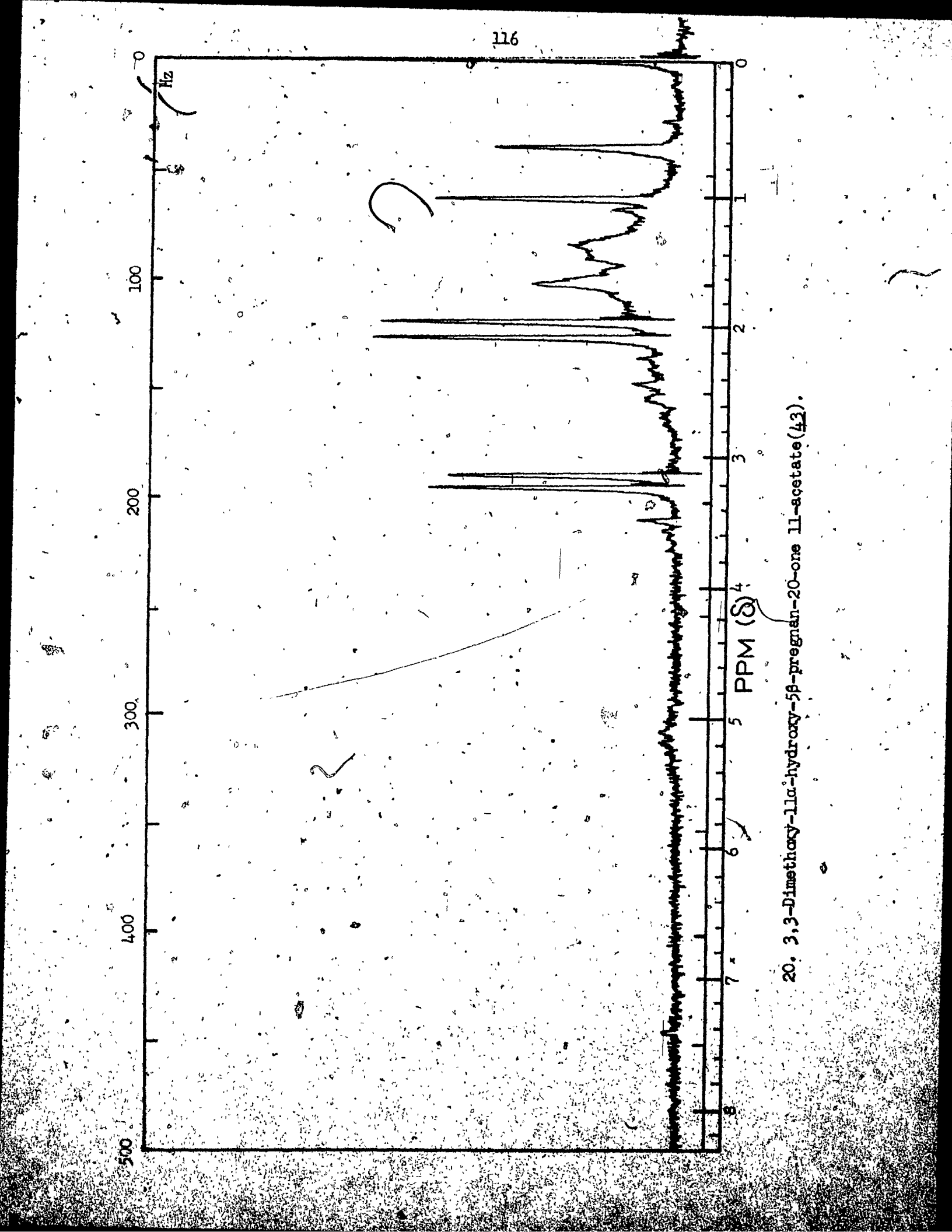
17. 18-Oximino-20β-hydroxy-5β-pregnan-3-one cyclic 3-(ethylene acetal)(33b).



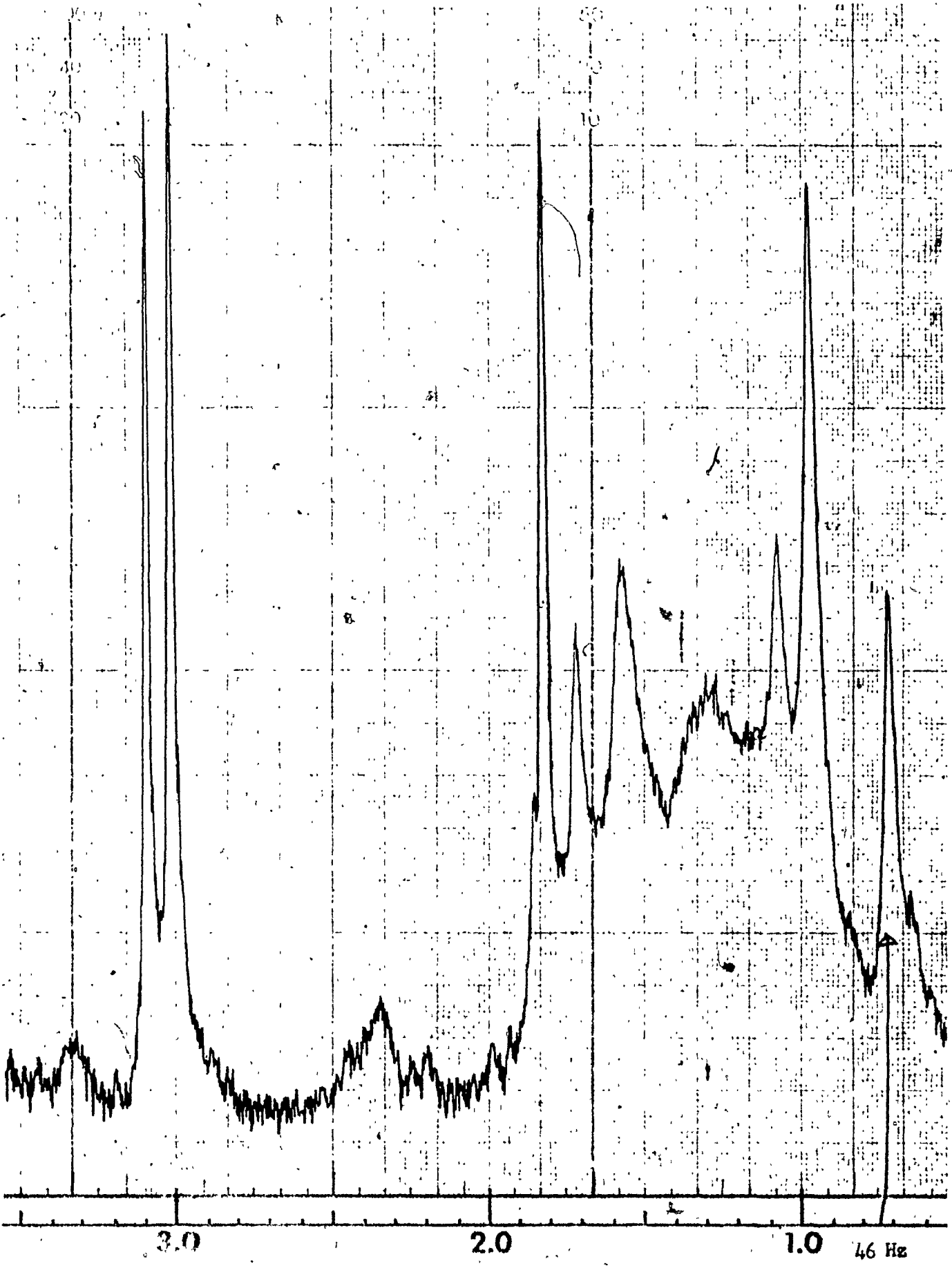
18. 11α-Hydroxypregn-4-ene-3,20-dione 11-acetate(41).



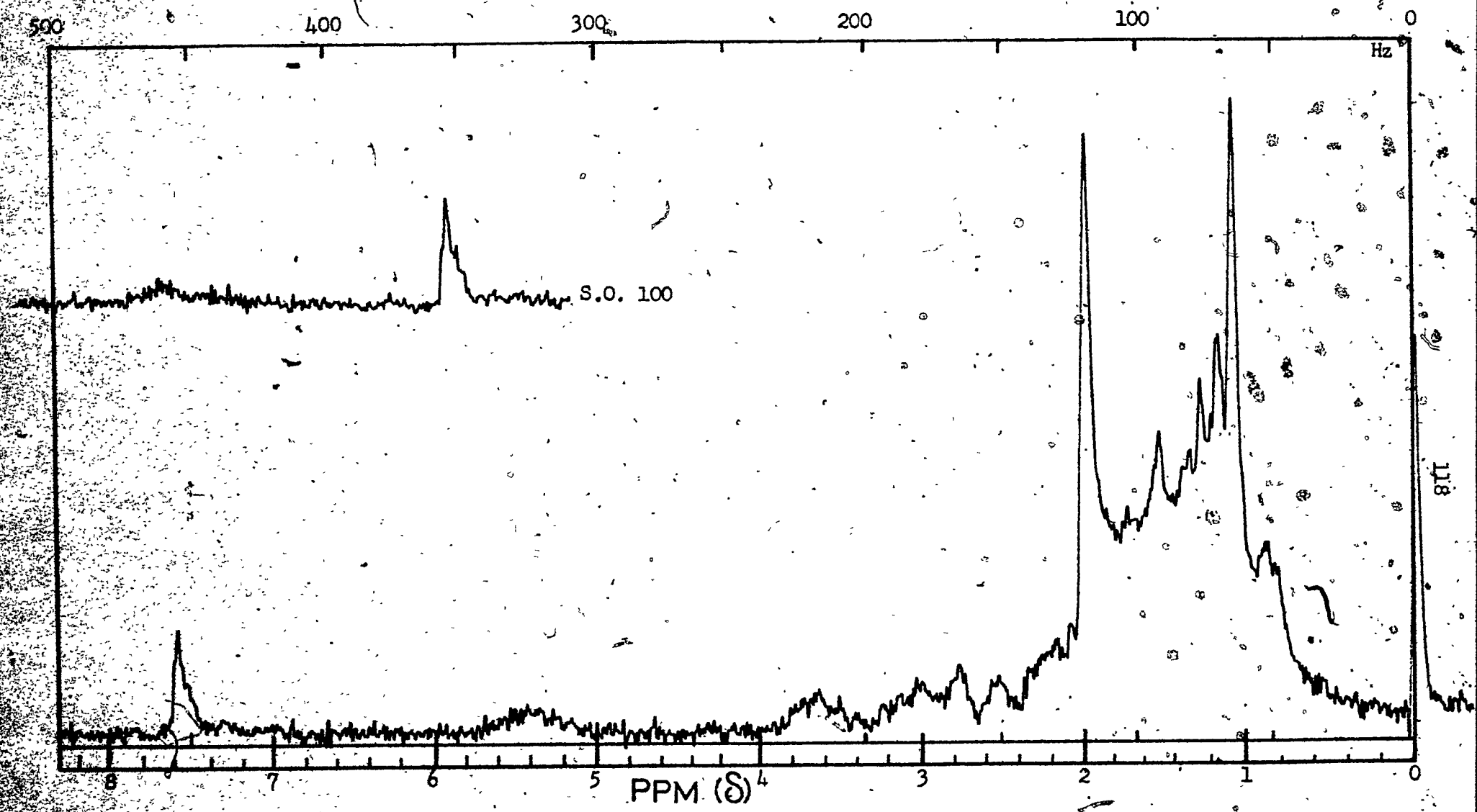
19. 11α-Hydroxy-5β-pregnane-3,20-dione 11-acetate(42).



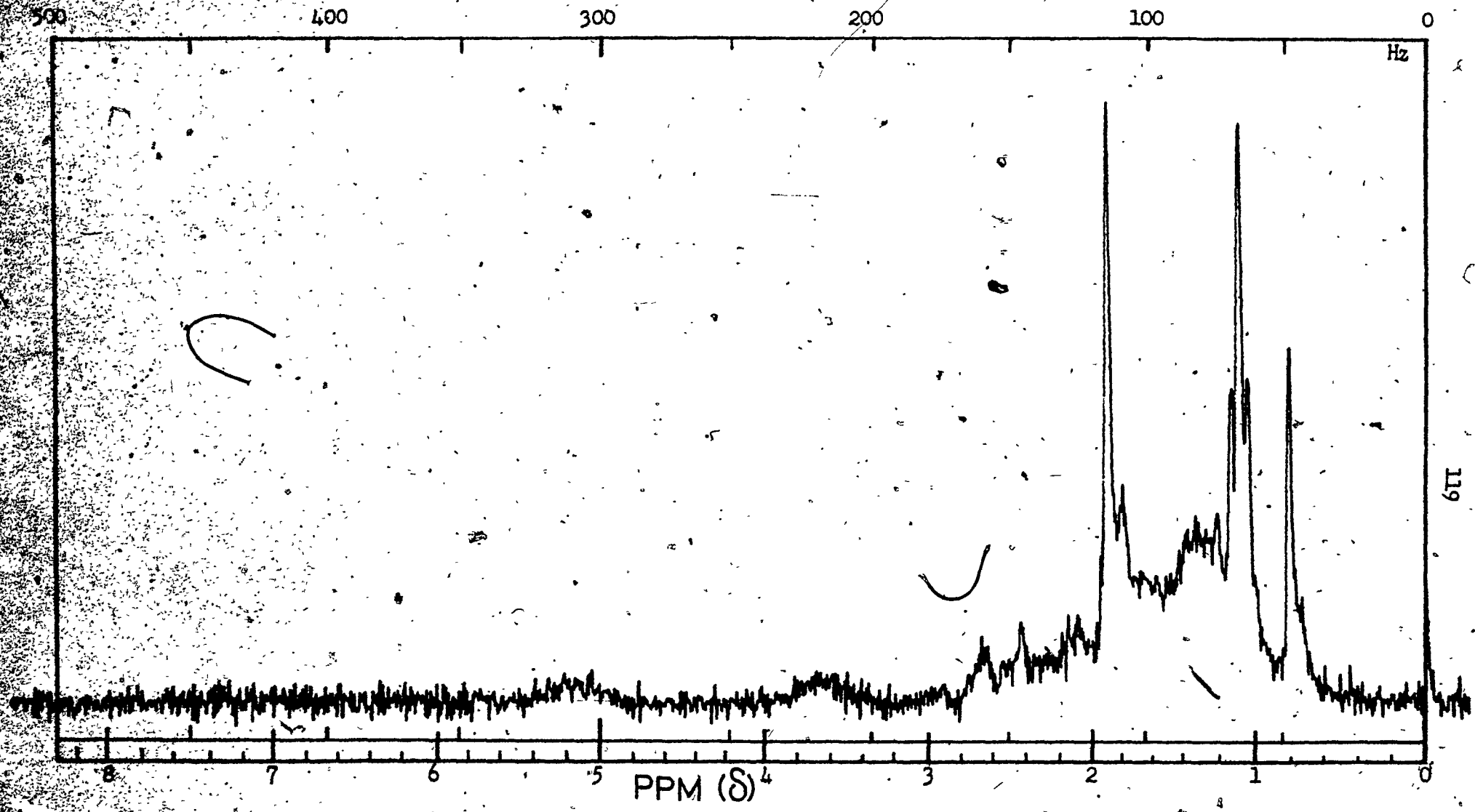
20. 3,3-Dimethoxy-11α-hydroxy-5β-pregnan-20-one 11-acetate(43).



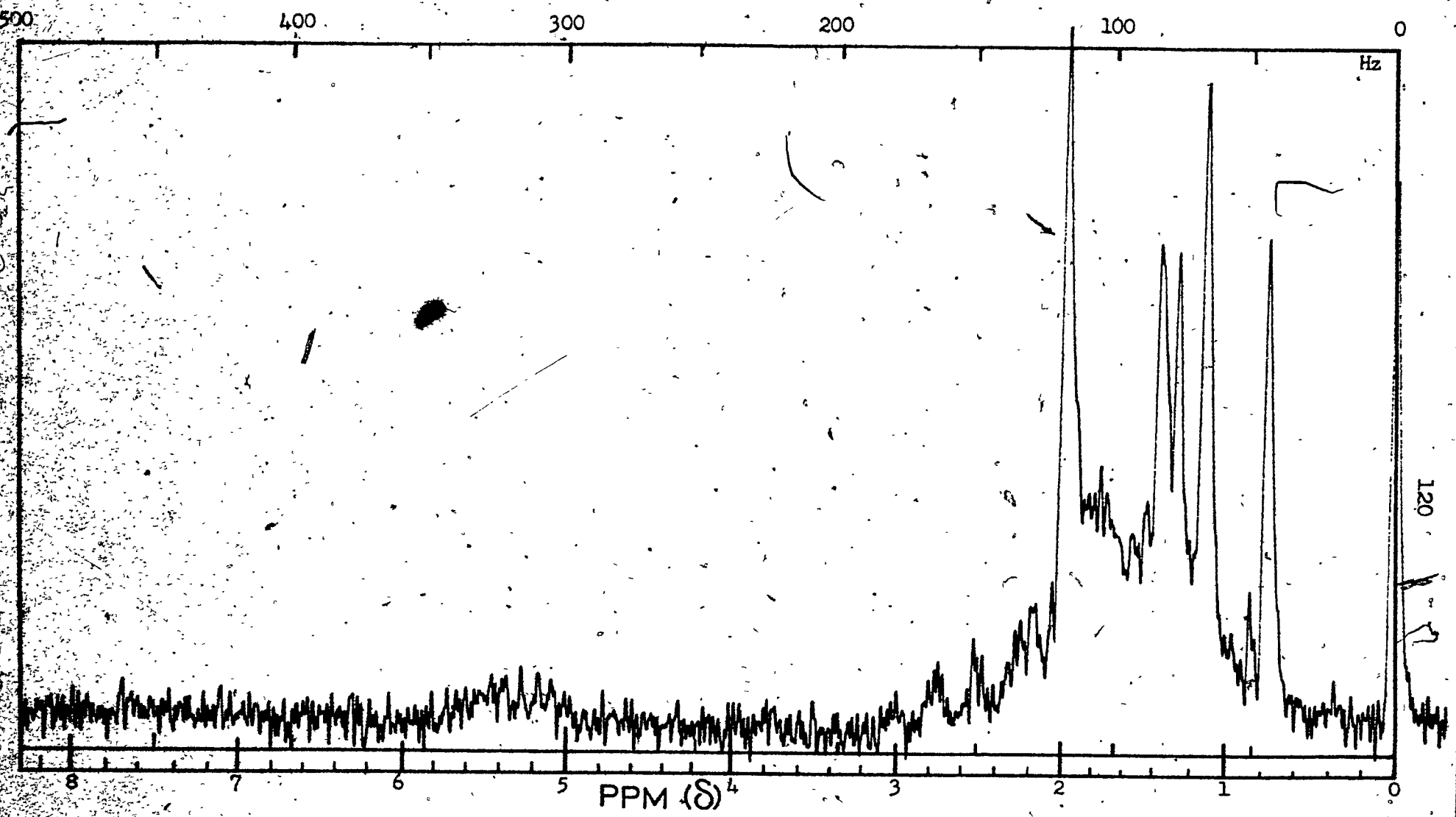
21. 3,3-Dimethoxy-5β-pregnane-11α,20β-diol 11-acetate(44).



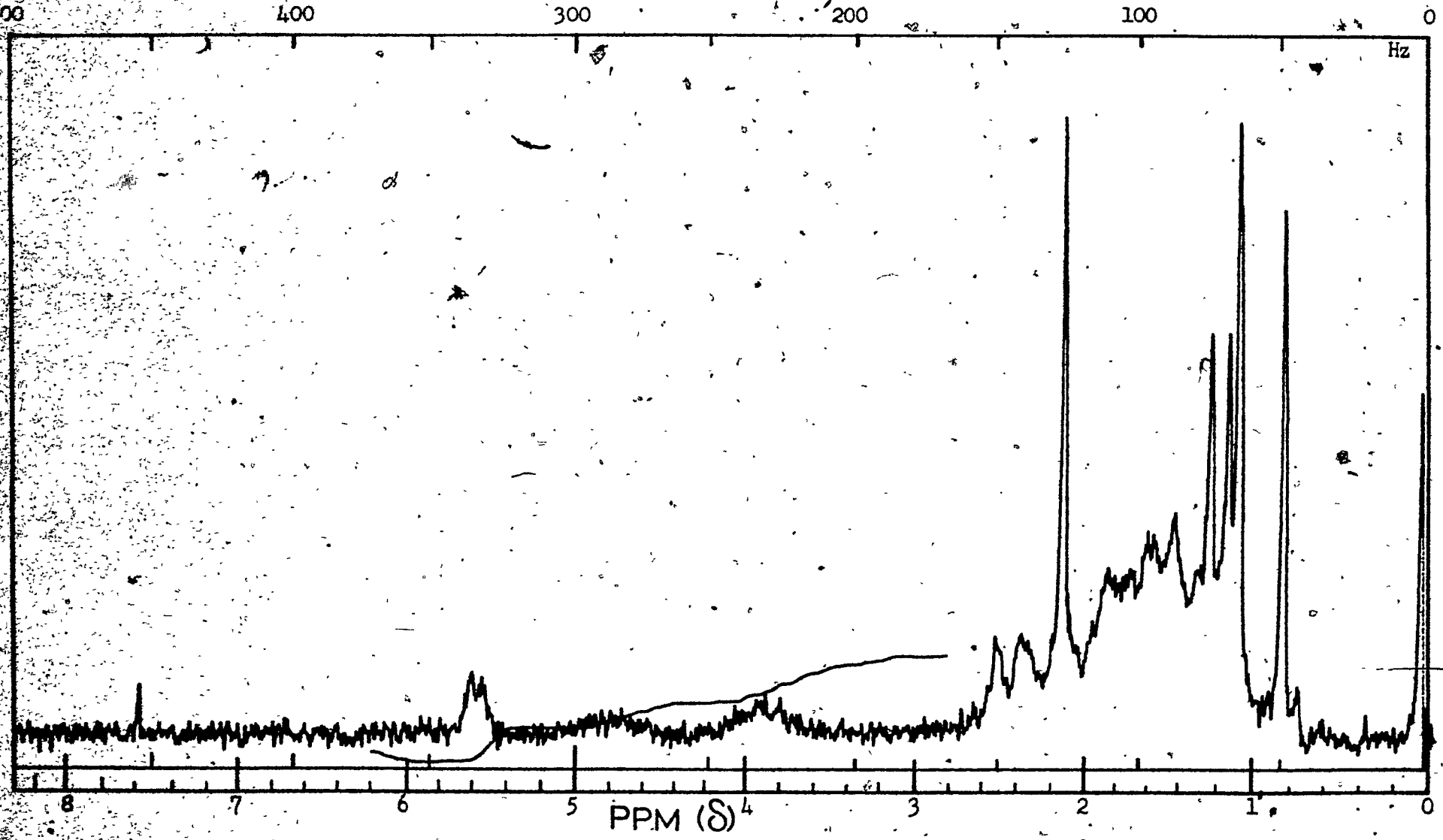
22. 18-Oximino-11α,20β-dihydroxy-5β-pregnan-3-one 11-acetate(46).



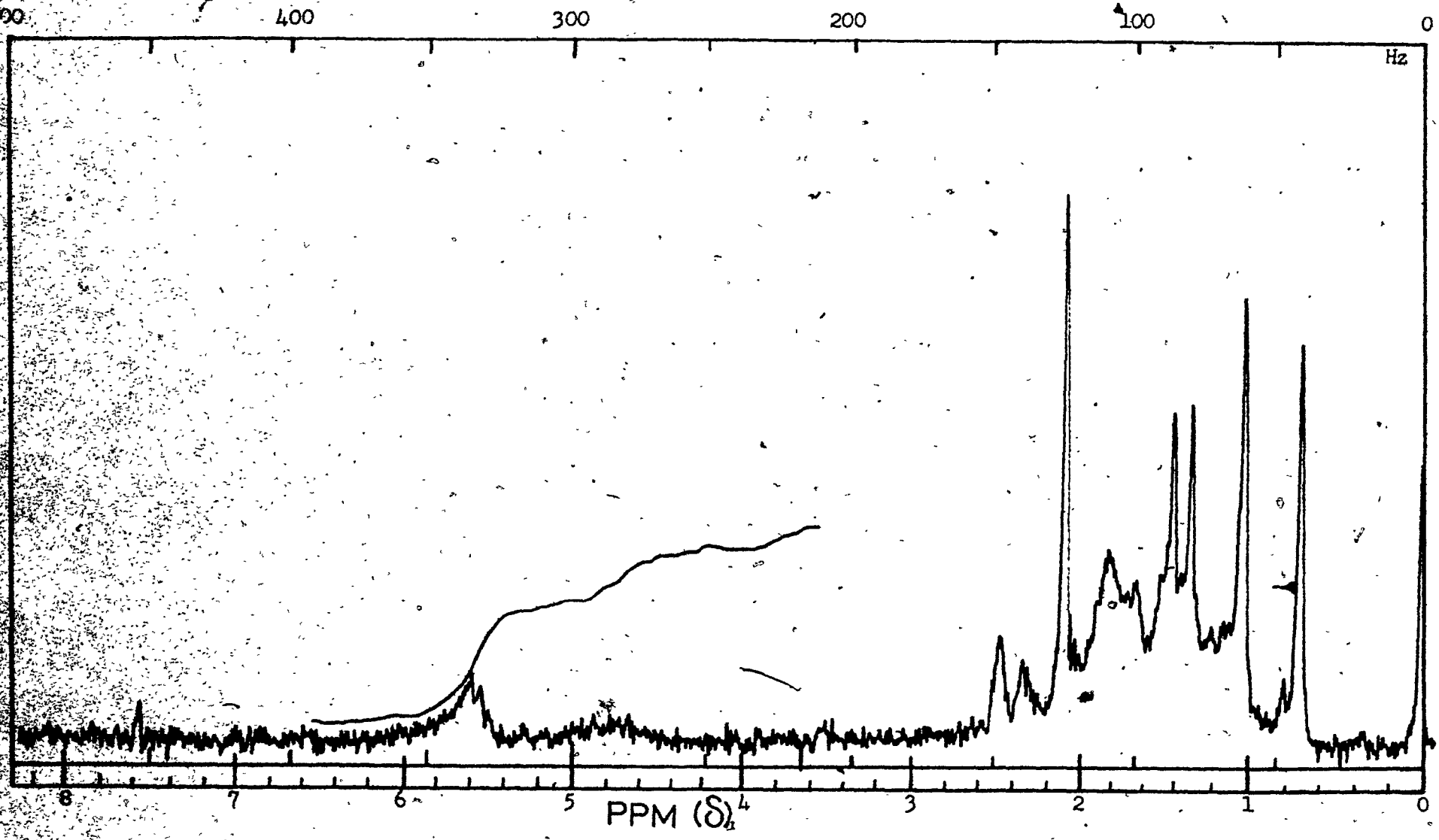
23. 11α,20β-Dihydroxy-5β-pregnan-3-one 11-acetate(47).



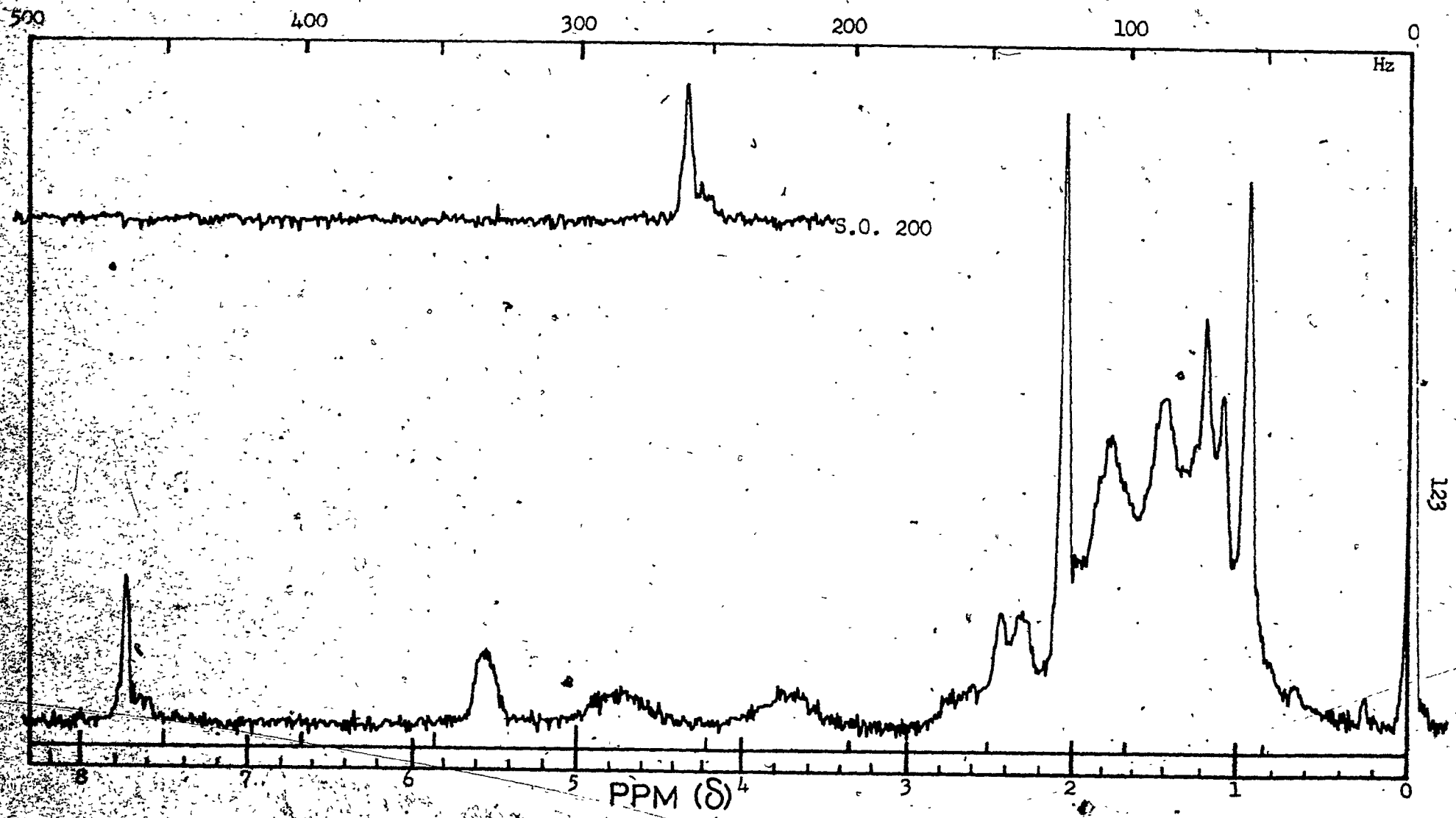
24. 11α,20β-Dihydroxy-5β-pregnan-3-one 11-acetate, 20-nitrite ester(48).



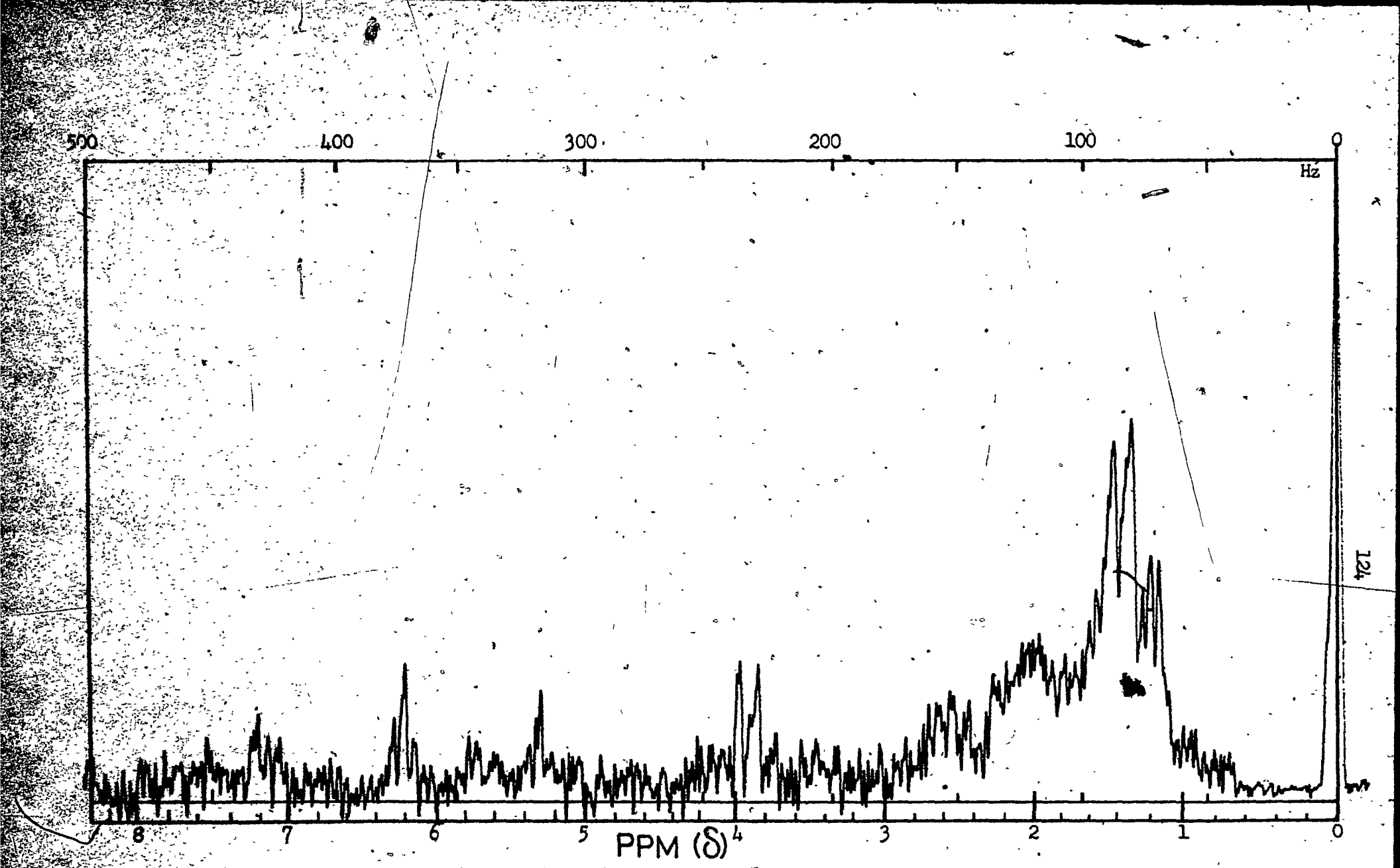
25. Pregn-5-ene-3β,20β-diol 3-acetate(50).



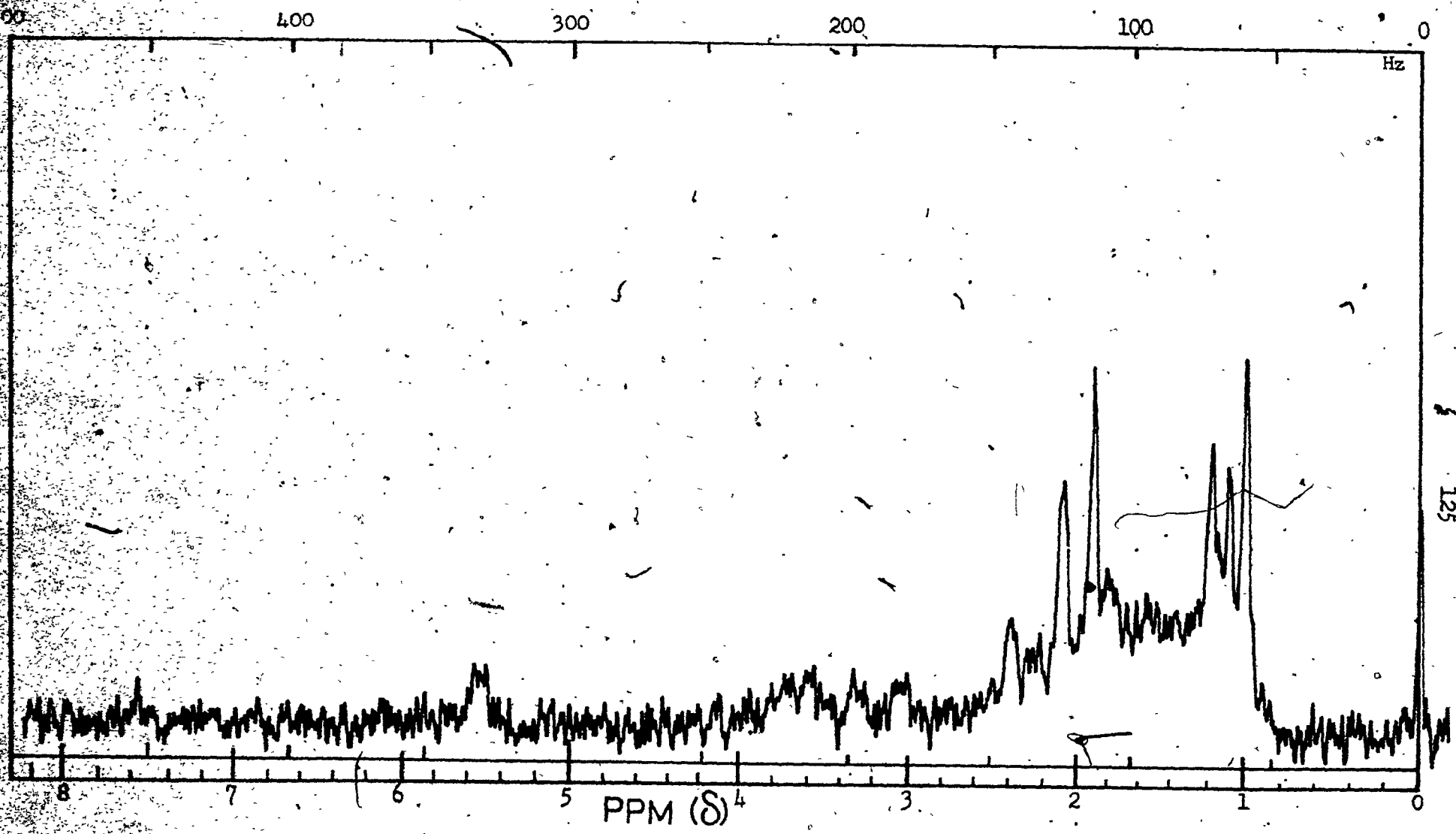
26. Pregn-5-ene-3β,20β-diol 3-acetate, 20-nitrite ester(51).



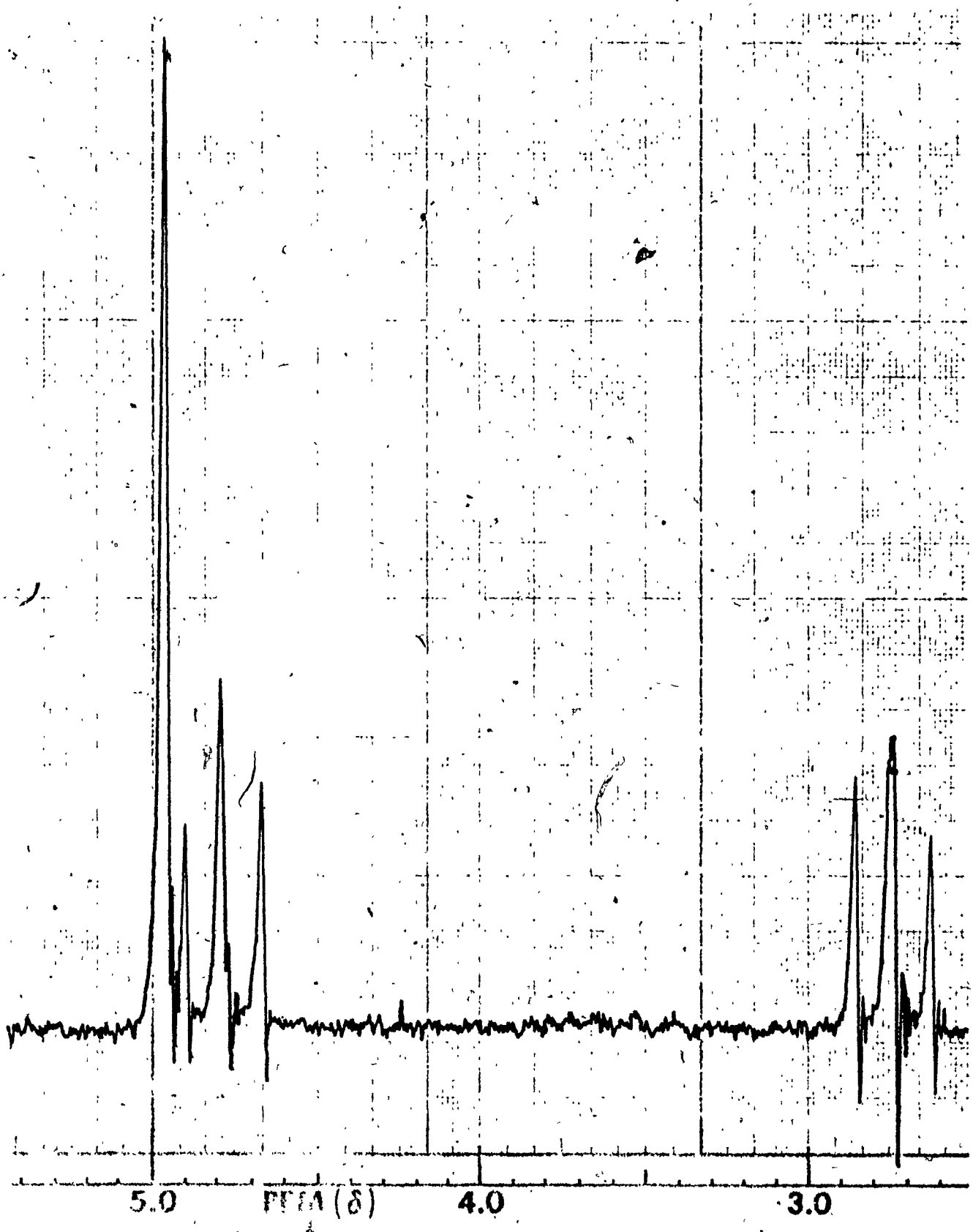
27. 18-Oximinopregn-5-ene-3β,20β-diol 3-acetate(52).



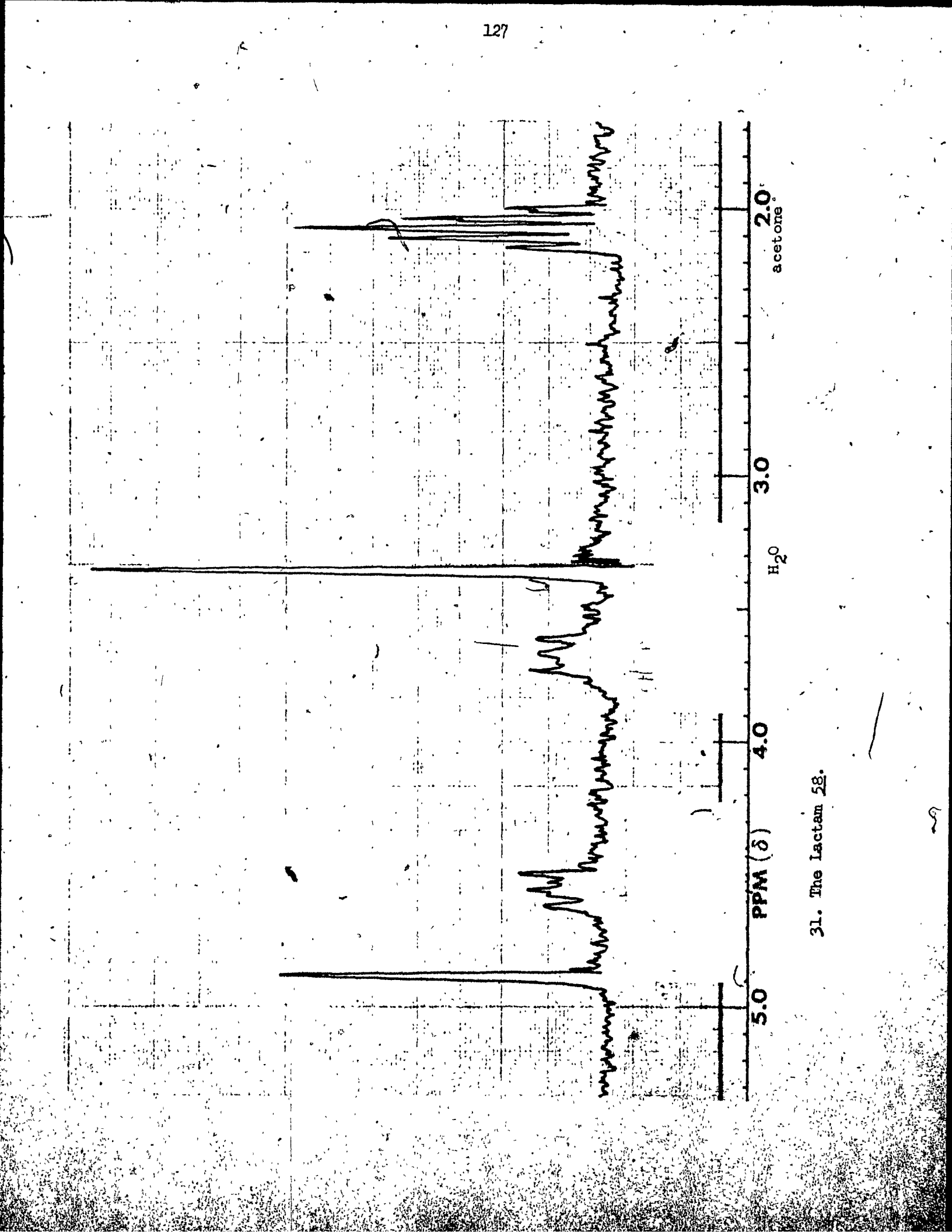
28. 18-Aminopregn-5-ene-3β,20β-diol(53)($C_2F_5CO_2H$)



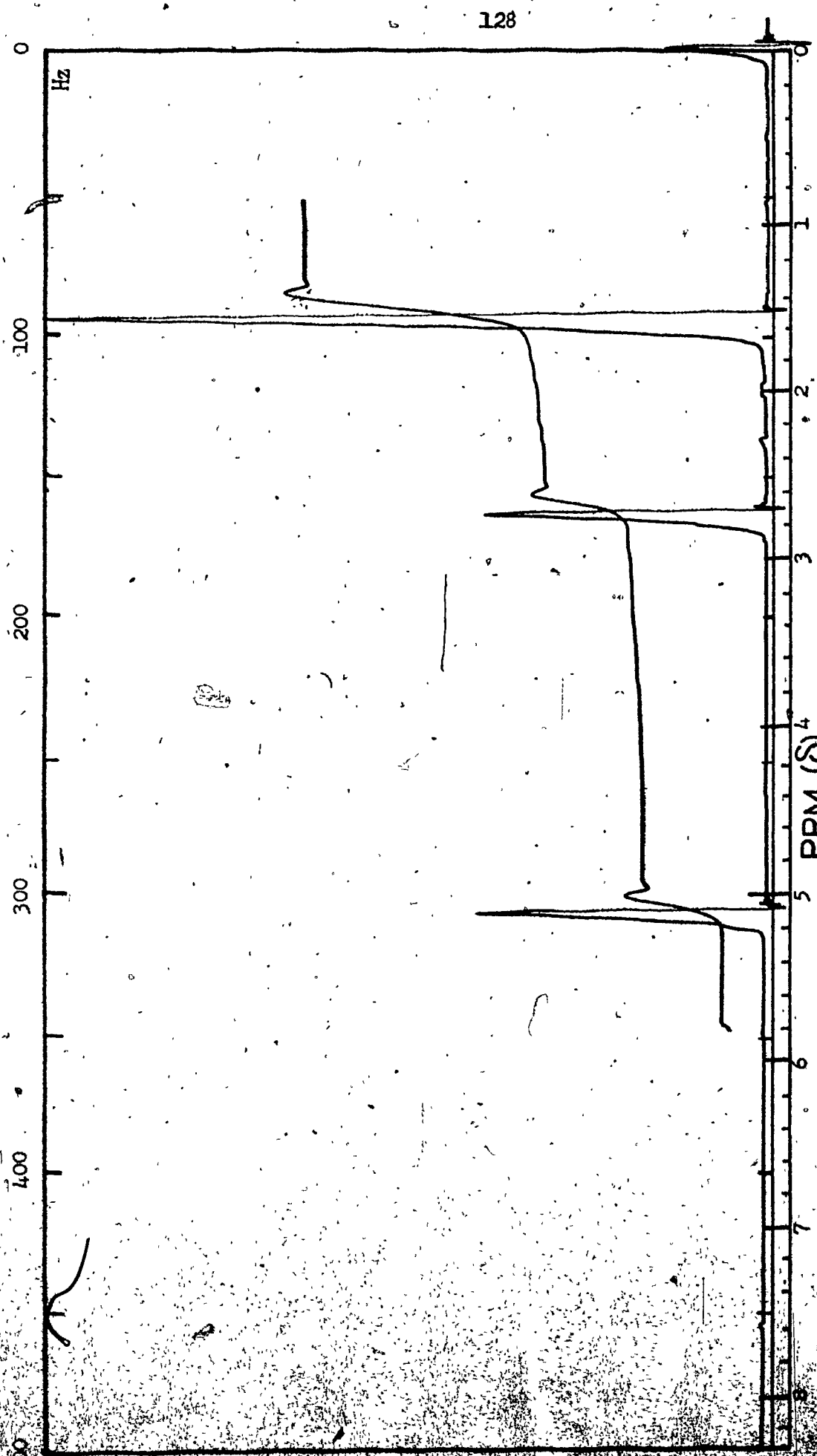
29. 18-Aminopregn-5-ene-3β,20β-diol 18-N-isopropylidene derivative(54).



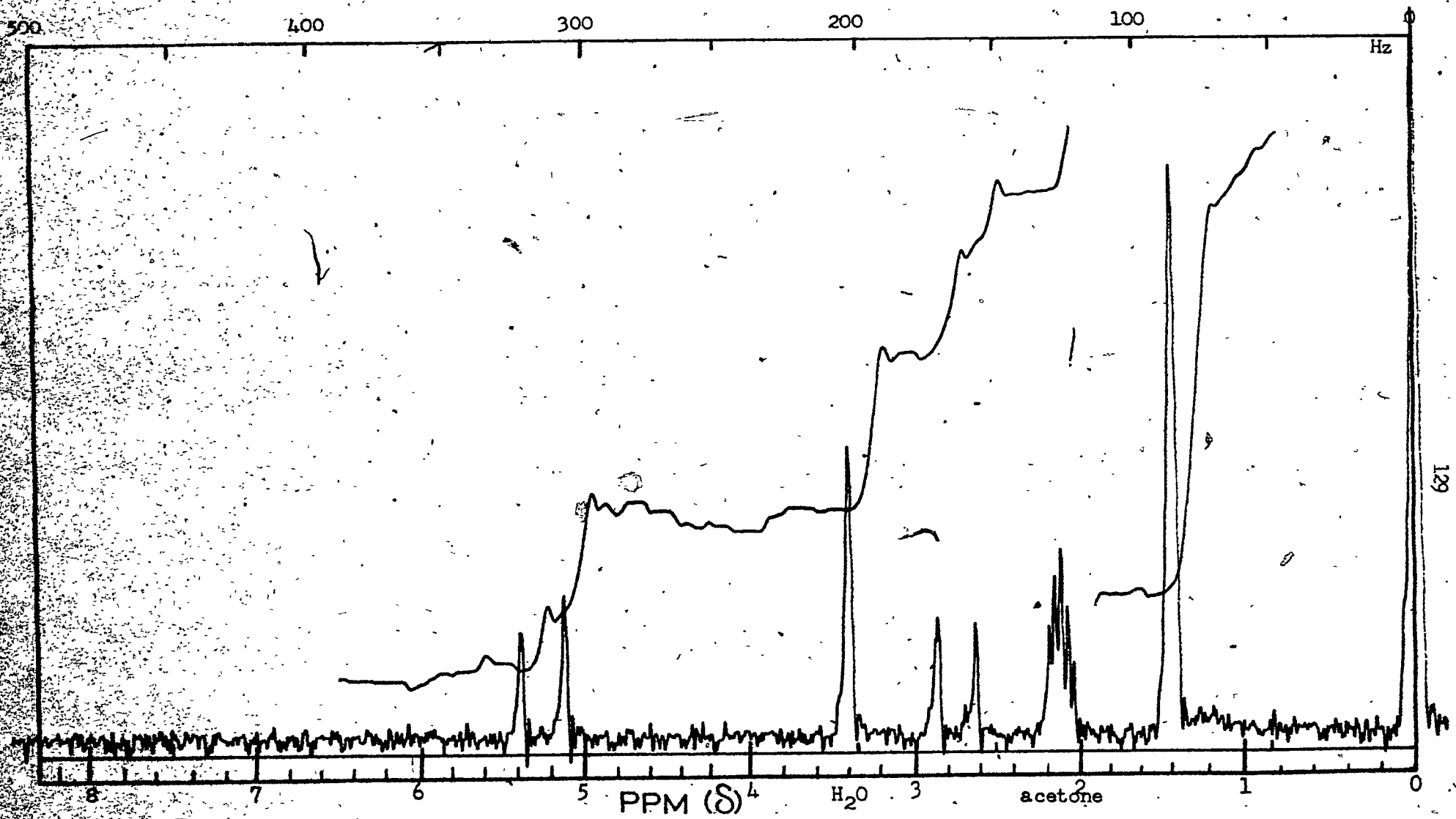
30. 3-Hydroxymethyl-5,6-dihydro-γ-pyrone-carboxylic acid-2 Lactone (57).



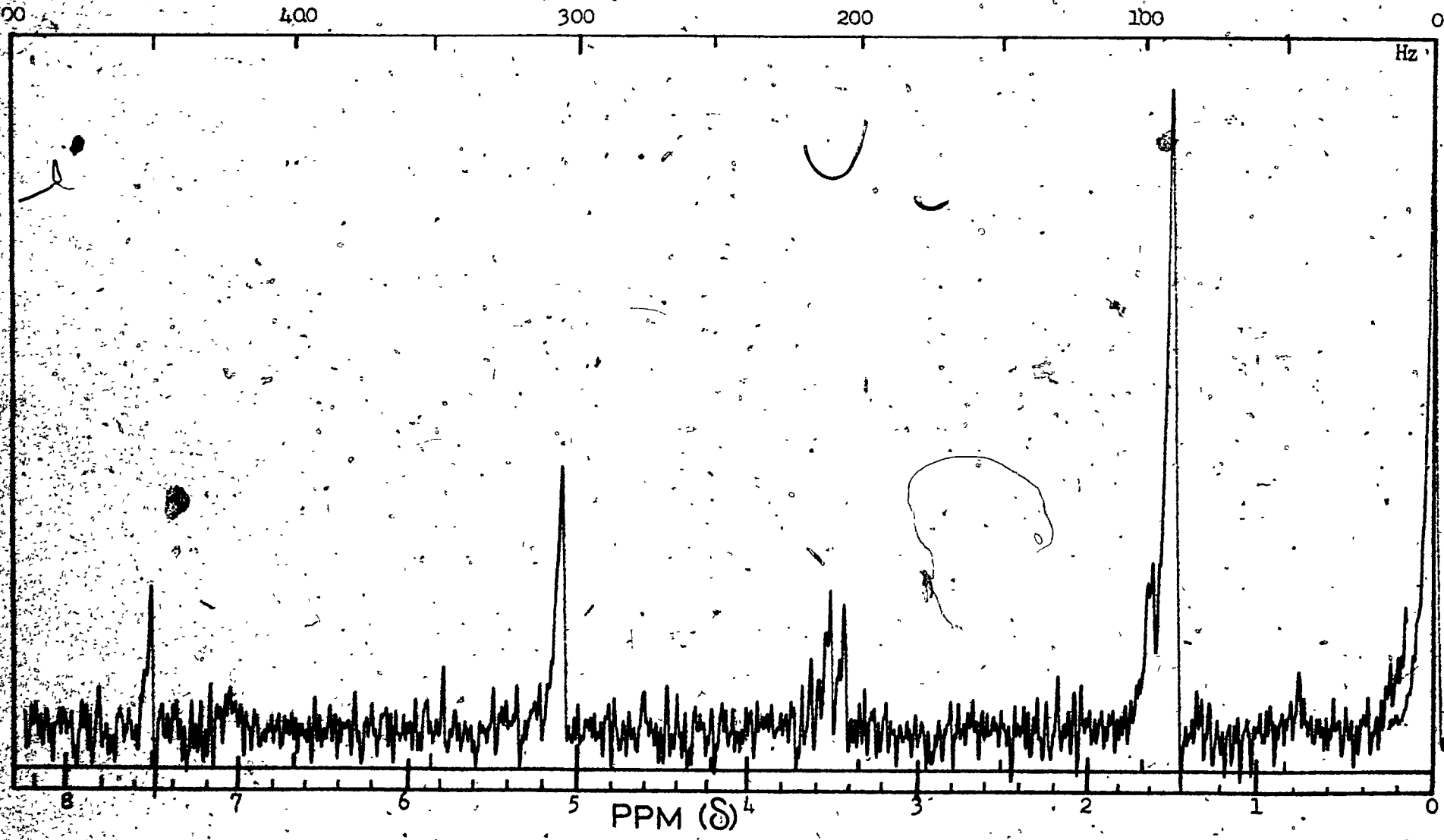
31. The Lactam 58.



32. 3-Hydroxymethyl-5,6-dihydro-6,6-dimethyl-γ-pyrone-carboxylic acid-2 Lactone(60).



33. The oxime 61(a and b).



34. The lactam ~~32~~.